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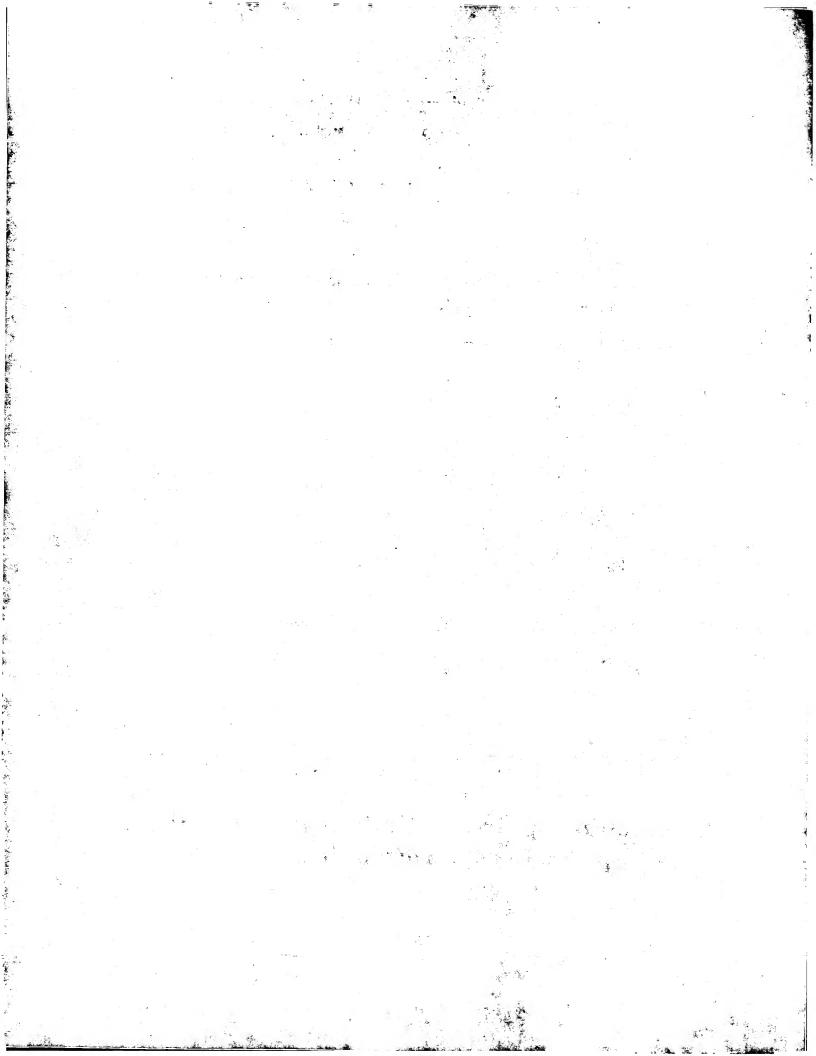
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(57) Abstract

The present invention relates to enhancer peptide sequences originally derived from various retroviral envelope (gp41) protein sequences that enhance the pharmacokinetic properties of any core polypeptide to which they are linked. The invention is based on the discovery that hybrid polypeptides comprising the enhancer peptide sequences linked to a core polypeptide possess enhanced pharmacokinetic properties such as increased half life. The invention further relates to methods for enhancing the pharmacokinetic properties of any core polypeptide through linkage of the enhancer peptide sequences to the core polypeptide. The core polypeptides to be used in the practice of the invention can include any pharmacologically useful peptide that can be used, for example, as a therapeutic or prophylactic reagent.

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HYBRID POLYPEPTIDES WITH ENHANCED PHARMACOKINETIC PROPERTIES

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1. <u>INTRODUCTION</u>

The present invention relates to enhancer peptide sequences originally derived from various retroviral envelope (gp41) protein sequences that enhance the pharmacokinetic properties of any core polypeptide to which they are linked. 15 The invention is based, in part, on the discovery that hybrid polypeptides comprising the enhancer peptide sequences linked to a core polypeptide possess enhanced pharmacokinetic properties such as increased half life. The invention further relates to novel anti-fusogenic and/or anti-viral, peptides, including ones that contain such enhancer peptide 20 sequences, and methods for using such peptides. invention further relates to methods for enhancing the pharmacokinetic properties of any core polypeptide through linkage of the enhancer peptide sequences to the core polypeptide. The core polypeptides to be used in the practice of the invention can include any pharmacologically 25 useful peptide that can be used, for example, as a therapeutic or prophylactic reagent. In a non-limiting embodiment, the invention is demonstrated by way of example wherein a hybrid polypeptide comprising, for example, an HIV core polypeptide linked to enhancer peptide sequences, is shown to be a potent, non-cytotoxic inhibitor of HIV-1, HIV-2

30 and SIV infection. Additionally, the enhancer peptide sequences of the invention have been linked to a respiratory

syncytial virus (RSV) core polypeptide and a luteinizing hormone receptor (LH-RH) core polypeptide. In each instance, the hybrid polypeptide was found to possess enhanced pharmacokinetic properties, and the RSV hybrid polypeptide exhibited substantial anti-RSV activity.

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2. BACKGROUND OF THE INVENTION

Polypeptide products have a wide range of uses as therapeutic and/or prophylactic reagents for prevention and treatment of disease. Many polypeptides are able to regulate biochemical or physiological processes to either prevent disease or provide relief from symptoms associated with disease. For example, polypeptides such as viral or bacterial polypeptides have been utilized successfully as vaccines for prevention of pathological diseases. Additionally, peptides have been successfully utilized as therapeutic agents for treatment of disease symptoms. Such peptides fall into diverse categories such, for example, as hormones, enzymes, immunomodulators, serum proteins and cytokines.

For polypeptides to manifest their proper biological and therapeutic effect on the target sites, the polypeptides must be present in appropriate concentrations at the sites of action. In addition, their structural integrity must generally be maintained. Therefore, the formulation of polypeptides as drugs for therapeutic use is directed by the chemical nature and the characteristics of the polypeptides, such as their size and complexity, their conformational requirements, and their often complicated stability, and solubility profiles. The pharmacokinetics of any particular therapeutic peptide is dependent on the bioavailability, distribution and clearance of said peptide.

Since many bioactive substances, such as peptides and proteins, are rapidly destroyed by the body, it is critical to develop effective systems for maintaining a steady concentration of peptide in blood circulation, to increase

the efficacy of such peptides, and to minimize the incidence and severity of adverse side effects.

3. SUMMARY OF THE INVENTION

The present invention relates, first, to enhancer 5 peptide sequences originally derived from various retroviral envelope (gp41) protein sequences i.e., HIV-1, HIV-2 and SIV, that enhance the pharmacokinetic properties of any core polypeptide to which they are linked. The invention is based on the surprising result that when the disclosed enhancer peptide sequences are linked to any core polypeptide, the 10 resulting hybrid polypeptide possesses enhanced pharmacokinetic properties including, for example, increased half life and reduced clearance rate relative to the core polypeptide alone. The present invention further relates to such hybrid polypeptides and core polypeptides, and to novel peptides that exhibit anti-fusogenic activity, antiviral 15 activity and/or the ability to modulate intracellular processes that involve coiled-coil peptide structures. Among such peptides are ones that contain enhancer peptide sequences.

Core polypeptides can comprise any peptides which may be introduced into a living system, for example, any peptides

20 capable of functioning as therapeutic, prophylactic or imaging reagents useful for treatment or prevention of disease or for diagnostic or prognostic methods, including methods in vivo imaging. Such peptides include, for example, growth factors, hormones, cytokines, angiogenic growth factors, extracellular matrix polypeptides, receptor ligands, agonists, antagonists or inverse agonists, peptide targeting agents, such as imaging agents or cytotoxic targeting agents, or polypeptides that exhibit antifusogenic and/or antiviral activity, and peptides or polypeptides that function as antigens or immunogens including, for example, viral and bacterial polypeptides.

The invention further relates to methods for enhancing the pharmacokinetic properties of any core polypeptide

through linkage of the core polypeptide to the enhancer peptide sequences to form hybrid polypeptides.

The invention still further relates to methods for using the peptides disclosed herein, including hybrid polypeptides containing enhancer peptide sequences. For example, the methods of the invention include methods for decreasing or inhibiting viral infection, e.g., HIV-1, HIV-2, RSV, measles, influenza, parainfluenza, Epstein-Barr, and hepatitis virus infection, and/or viral-induced cell fusion events. The enhancer peptide sequences of the invention can, additionally, be utilized to increase the in vitro or ex-vivo half-life of a core polypeptide to which enhancer peptide sequences have been attached, for example, enhancer peptide sequences can increase the half life of attached core polypeptides in cell culture or cell or tissue samples.

The invention is demonstrated by way of examples wherein hybrid polypeptides containing an HIV core polypeptide linked to enhancer peptide sequences are shown to exhibit greatly enhanced pharmacokinetic properties and act as a potent, noncytotoxic inhibitors of HIV-1, HIV-2 and SIV infection. The invention is further demonstrated by examples wherein hybrid polypeptides containing an RSV core polypeptide or a luteinizing hormone polypeptide are shown to exhibit greatly enhanced pharmacokinetic properties. In addition, the RSV hybrid polypeptide exhibited substantial anti-RSV activity.

3.1. <u>DEFINITIONS</u>

Peptides, polypeptides and proteins are defined herein as organic compounds comprising two or more amino acids

covalently joined, e.g., by peptide amide linages. Peptides, polypeptide and proteins may also include non-natural amino acids and any of the modifications and additional amino and carboxyl groups as are described herein. The terms "peptide," "polypeptide" and "protein" are, therefore, utilized interchangeably herein.

Peptide sequences defined herein are represented by oneletter symbols for amino acid residues as follows:

```
A (alanine)
   R (arginine)
   N (asparagine)
   D (aspartic acid)
   C (cysteine)
   Q (glutamine)
  E (glutamic acid)
 5 G (glycine)
  H (histidine)
   I (isoleucine)
  L (leucine)
  K (lysine)
  M (methionine)
  F (phenylalanine)
  P (proline)
  S (serine)
10 T (threonine)
  W (tryptophan)
  Y (tyrosine)
  V (valine)
  X (any amino acid)
```

"Enhancer peptide sequences" are defined as peptides having the following consensus amino acid sequences: "WXXWXXXI", "WXXWXXX", "WXXWXX", "WXXXWX", "WXXXWXWX", "XXXWXWX", "XXWXWX", "XWXWX", "WXXXXWXW", "WXXXXWX", "WXXXW", "IXXXWXXW", "XXXWXXW", "XXWXXW", "XWXWXXXW", "XWXWXXX", "XWXWXX", "XWXWX", "XWXW", "WXWXXXW", or "XWXXXW", wherein X can be any amino acid, W represents / tryptophan and I represents isoleucine. As discussed below, 20 the enhancer peptide sequences of the invention also include peptide sequences that are otherwise the same as the consensus amino acid sequences but contain amino acid substitutions, insertions or deletions but which do not abolish the ability of the peptide to enhance the pharmacokinetic properties of a core peptide to which it is linked relative to the pharmacokinetic properties of the core polypeptide alone.

"Core polypeptide" as used herein, refers to any polypeptide which may be introduced into a living system and, thus, represents a bioactive molecule, for example any polypeptide that can function as a pharmacologically useful peptide for treatment or prevention of disease.

"Hybrid polypeptide" as used herein, refers to any polypeptide comprising an amino, carboxy, or amino and carboxy terminal enhancer peptide sequence and a core polypeptide. Typically, an enhancer peptide sequence is linked directly to a core polypeptide. It is to be understood that an enhancer peptide can also be attached to an intervening amino acid sequence present between the enhancer peptide sequence and the core peptide.

"Antifusogenic" and "anti-membrane fusion," as used herein, refer to a peptide's ability to inhibit or reduce the level of fusion events between two or more structures e.g.,

10 cell membranes or viral envelopes or pili, relative to the level of membrane fusion which occurs between the structures in the absence of the peptide.

"Antiviral," as used herein, refers to the peptide's ability to inhibit viral infection of cells via, <u>e.g.</u>, cell fusion or free virus infection. Such infection can involve membrane fusion, as occurs in the case of enveloped viruses, or another fusion event involving a viral structure and a cellular structure, <u>e.g.</u>, fusion of a viral pilus and bacterial membrane during bacterial conjugation).

4. BRIEF DESCRIPTION OF DRAWINGS

- FIG. 1. Hybrid polypeptides. Enhancer peptide sequences derived from putative N-terminal and C-terminal interactive regions are depicted linked to a generic core polypeptide. Conserved enhancer peptide sequences are shaded. It is to be noted that the enhancer peptide sequences indicated may be used either as terminal, C-terminal, or and C-terminal additions. Further, the enhancer peptide sequences can be added to a core polypeptide in forward or reverse orientation, individually or in any of the possible combinations, to enhance pharmacokinetic properties of the peptide.
- FIG. 2A. Enhancer peptide sequences derived from various envelope (gp41) protein sequences, representing the

N-terminal interactive region observed in all currently published isolate sequences of HIV-1, HIV-2 and SIV. The final sequence "WXXWXXXI" represents a consensus sequence.

- FIG. 2B. Enhancer peptide sequence variants derived from various envelope (gp41) protein sequences, representing the C-terminal interactive region observed in all currently published isolate sequences of HIV-1, HIV-2 and SIV. The final sequence "WXXXWXWX" represents a consensus sequence.
- FIG. 3. Comparison of HIV-1 titres in tissues of HIV-1

 10 9320 infected SCID-HuPBMC mice as measured by P24 Levels in
 HuPBMC co-culture assays. The figure shows a comparison of
 in vivo T20 and T1249 viral inhibition.
- FIG. 4A-4B. Plasma pharmacokinetic profile of T1249 vs.
 T1387 core control in CD-rats following IV injection for up

 15 to 2 hrs (FIG. 4A) and 8 hrs (FIG. 4B). The T1387
 polypeptide is a core polypeptide and the T1249 polypeptide
 is the core polypeptide linked to enhancer peptide sequences.
- FIG. 5. Plasma pharmacokinetic profile of T1249 vs. T20 control in CD-rats following IV administration. The T1249

 20 polypeptide is a hybrid polypeptide of a core polypeptide (T1387) linked to enhancer peptide sequences. T20: n=4;
 T1249: n=3.
 - FIG. 6. Comparison of T20/T1249 Anti-HIV-1/IIIb activity and cytotoxicity.

FIG. 7. Direct Binding of T1249 to gp41 construct M41 Δ 178. ¹²⁵I-T1249 was HPLC purified to maximum specific activity. Saturation binding to M41 Δ 178 (a gp41 ectodomain fusion protein lacking the T20 amino acid sequence) immobilized in microtitre plates at 0.5 mg/ml is shown.

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FIG. 8. Time Course of T1249 Association/Dissociation. The results demonstrate that ¹²⁵I-T1249 and ¹²⁵I-T20 have similar binding affinities of 1-2 nM. Initial on and off rates for ¹²⁵I-T1249 were significantly slower than those of 125I-T20. Dissociation of bound radioligand was measured following the addition of unlabeled peptide to a final concentration of 10µm in 1/10 total assay volume.

- FIG. 9. Competition for T1249 Binding to M41\(\Delta\)178.

 Unlabeled T1249 and T20 were titrated in the presence of a single concentration of either \(^{125}I\)-T1249 or \(^{125}I\)-T20. Ligand was added just after the unlabeled peptide to start the incubation.
 - FIG. 10A-10B. Plasma pharmacokinetic profile of RSV hybrid polypeptides T1301 (10A) and T1302 (10B) vs. T786 in CD rats.

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- FIG. 11A. Plaque Reduction Assay. Hybrid polypeptide T1293 is capable of inhibiting RSV infection with an IC₅₀ 2.6 μ g/ml.
- FIG. 11B. Plaque Reduction Assay demonstrates the ability of RSV Hybrid Polypeptides T1301, T1302 and T1303 to inhibit RSV infection.
- FIG. 12A and 12B. Plasma pharmacokinetic profile of luteinizing hormone hybrid polypeptide T1324 vs T1323 in CD male rats. The T1323 polypeptide is a luteinizing hormone core polypeptide and the T1324 polypeptide is a hybrid polypeptide comprising a core polypeptide linked to enhancer peptide sequences.
- FIG. 13. Hybrid polypeptide sequences derived from various core polypeptides. Core polypeptide sequences are shown shaded. The non-shaded amino and carboxy terminal sequences represent enhancer peptide sequences.

FIG. 14A-B. Circular Dichroism (CD) spectra for T1249 in solution (phosphate buffered saline, pH 7) alone (10 µM at 1°C; FIG. 14A) and in combination with a 45-residue peptide from the gp41 HR1 binding domain (T1346); the closed square (*) represents a theoretical CD spectrum predicted for a 5 "non-interaction model" whereas the actual CD spectra are represented by the closed circle (*).

- FIG. 15. Polyacrylamide gel electrophoresis showing T1249 protection of the gp41 construct M41Δ178 from proteinase-K digestion; lane 1: primer marker; lane 2: untreated M41Δ178; lane 3: M41Δ178 incubated with proteinase-K; lane 4: untreated T1249; lane 5: T1249 incubated with proteinase-K; lane 6: M41Δ178 incubated with T1249; lane 7: incubation of T1249 and M41Δ178 prior to addition of proteinase-K.
- albino rats; FIG. 16A: pharmacokinetics of T1249 in Sprague-Dawley albino rats; FIG. 16A: pharmacokinetics of T1249 in a single dose administration by continuous subcutaneous infusion; FIG. 16B: Plasma pharmacokinetics of T1249 administered by subcutaneous injection (SC) or intravenous injection IV); FIG. 16C: Kinetic analysis of T1249 in lymph and plasma after intravenous administration.
- FIG. 17A-B Pharmacokinetics of T1249 in cynomolgus monkeys; FIG. 17A: plasma pharmacokinetics of a single 0.8 mg/kg dose of T1249 via subcutaneous (SC) intravenous (IV) or intramuscular (IM) injection; FIG. 17B: Plasma pharmacokinetics of subcutaneously administered T1249 at three different dose levels (0.4 mg/kg, 0.8 mg/kg, and 1.6 mg/kg).

5. DETAILED DESCRIPTION OF THE INVENTION

Described herein are peptide sequences, referred to as enhancer peptide sequences, derived from various retroviral

envelope (gp41) protein sequences that are capable of enhancing the pharmacokinetic properties of core polypeptides to which they are linked. Such enhancer peptide sequences can be utilized in methods for enhancing the pharmacokinetic properties of any core polypeptide through linkage of the enhancer peptide sequences to the core polypeptide to form a hybrid polypeptide with enhanced pharmacokinetic properties relative to the core polypeptide alone. The half life of a core peptide to which an enhancer peptide sequence or sequences has been attached can also be increased in vitro. For example, attached enhancer peptide sequences can increase the half life of a core polypeptide when present in cell culture, tissue culture or patient samples, such as cell, tissue, or other samples.

The core polypeptides of the hybrid polypeptides of the invention comprise any peptide which may be introduced into a living system, for example, any peptide that can function as a therapeutic or prophylactic reagent useful for treatment or prevention of disease, or an imaging agent useful for imaging structures in vivo.

Also described herein are peptides, including peptides that contain enhancer peptide sequences, that exhibit antifusogenic and/or anti-viral activity. Further described herein are methods for utilizing such peptides, including methods for decreasing or inhibiting viral infection and/or viral induced cell fusion.

5.1. HYBRID POLYPEPTIDES

The hybrid polypeptides of the invention comprise at
least one enhancer peptide sequence and a core polypeptide.
Preferably, the hybrid polypeptides of the invention comprise
at least two enhancer peptide sequences and a core
polypeptide, with at least one enhancer peptide present in
the hybrid polypeptide amino to the core polypeptide and at
least one enhancer peptide sequence present in the hybrid
polypeptide carboxy to the core polypeptide.

The enhancer peptide sequences of the invention comprise peptide sequences originally derived from various retroviral envelope (gp 41) protein sequences, including HIV-1, HIV-2 and SIV sequences, and specific variations or modifications thereof described below. A core polypeptide can comprise any 5 peptide sequence, preferably any peptide sequence that may be introduced into a living system, including, for example, peptides to be utilized for therapeutic, prophylactic or imaging purposes.

Typically, a hybrid polypeptide will range in length from about 10 to about 500 amino acid residues, with about 10 10 to about 100 amino acid residues in length being preferred, and about 10 to about 40 amino acids in length being most preferred.

While not wishing to be bound by any particular theory, the structure of the envelope protein is such that the putative α -helix region located in the C-terminal region of 15 the protein is believed to associate with the leucine zipper region located in the N-terminal region of the protein. Alignment of the N-terminal and C-terminal enhancer peptide sequence gp41 regions observed in all currently published isolate sequences of HIV-1, HIV-2 and SIV identified consensus amino acid sequences.

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In particular, the following consensus amino acid sequences representing consensus enhancer peptide sequences were identified (the consensus sequences are listed below in forward and reverse orientations because said enhancer peptide sequences can be utilized either in forward or reverse orientation): "WXXWXXXI", "WXXWXXX", 25 "WXXWX", "WXXW", "WXXXWXWX", "XXXWXWX", "XXWXWX", "XWXWX", "WXWX", "WXXXWXW", "WXXXWX", "IXXXWXXW", "XXXWXXW", "XXWXXW", "XWXXXW", "XWXXXXXW", "XWXXXXX", "XWXXXXX", "XWXXXXX", "XWXW", "WXWXXXW", or "XWXXXW", wherein X can be any amino acid, W represents tryptophan and I represents isoleucine. Forward orientations of consensus amino acid sequences are 30 shown in FIGS. 1 and 2.

Typically, an enhancer peptide sequence will be about 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29 or 30 amino acid residues in length, with about 4 to about 20 residues in length being preferred, about 4 to about 10 residues in length being more 5 preferred, and about 6 to about 8 residues in length being most preferred.

In a preferred embodiment of the invention, enhancer peptide sequences which may be used to enhance the pharmacokinetic properties of the resultant hybrid polypeptides comprise the specific enhancer peptide sequences depicted in FIGS. 2, 13, and Table 1, below. Among the most preferred enhancer peptide sequences are ones comprising the following amino sequence: "WQEWEQKI" and "WASLWEWF".

By way of example and not by way of limitation, Table 1, below, lists amino acid sequences that represent preferred embodiments of the enhancer peptide sequences of the enhancer peptide sequences of the invention. It is to be understood that while the forward orientation of these sequences is depicted below, the reverse orientation of the sequences is also intended to fall within the scope of the present invention. For example, while the forward orientation of the enhancer peptide sequence "WMEWDREI" is depicted below, its reverse orientation, i.e., "IERDWEMW" is also intended to be included.

TABLE 1

25

WMEWDREI
WQEWERKV
WQEWEQKV
MTWMEWDREI
NNMTWMEWDREI
WQEWEQKVRYLEANI
NNMTWQEWEZKVRYLEANI
WNWFI

30

WQEWDREISNYTSLI WQEWEREISAYTSLI WQEWDREI WQEWEI WNWF 5 WQEW WQAW WQEWEQKI WASLWNWF WASLFNFF WDVFTNWL 10 WASLWEWF **EWASLWEWF** WEWF **EWEWF IEWEWF IEWEW** 15 **EWEW** WASLWEWF WAGLWEWF AKWASLWEWF **AEWASLWEWF** WASLWAWF 20 **AEWASLWAWF AKWASLWAWF** WAGLWAWF **AEWAGLWAWF** WASLWAW AEWASLWAW 25 WAGLWAW **AEWAGLWAW** DKWEWF **IEWASLWEWF IKWASLWEWF** DEWEWF 30 **GGWASLWNWF**

GGWNWF

In another preferred embodiment, particular enhancer peptide sequences of the invention comprise the enhancer peptide sequences depicted in FIGS. 2, 13 and Table 1 exhibiting conservative amino acid substitutions at one, two or three positions, wherein said substitutions do not abolish the ability of the enhancer peptide sequence to enhance the pharmacokinetic properties of a hybrid polypeptide relative to its corresponding core polypeptide.

Most preferably, such substitutions result in enhancer peptide sequences that fall within one of the enhancer peptide sequence consensus sequences. As such, generally, the substitutions are made at amino acid residues corresponding to the "X" positions depicted in the consensus amino acid sequences depicted above and in FIGS. 1 and 2. "Conservative substitutions" refer to substitutions with amino acid residues of similar charge, size and/or hydrophobicity/hydrophilicity characteristics as the amino acid residue being substituted. Such amino acid characteristics are well known to those of skill in the art.

The present invention further provides enhancer peptide sequences comprising amino acid sequences of FIGS. 1, 2, 13 and Table 1 that are otherwise the same, but, that said enhancer peptide sequences comprise one or more amino acid additions (generally no greater than about 15 amino acid residues in length), deletions (for example, amino- or terminal- truncations) or non-conservative substitutions which nevertheless do not abolish the resulting enhancer peptide's ability to increase the pharmacokinetic properties of core polypeptides to which they are linked relative to core polypeptides without such enhancer peptide sequences.

Additions are generally no greater than about 15 amino acid residues and can include additions of about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 or 15 consecutive amino acid residues. Preferably the total number of amino acid residues added to the original enhancer peptide is no greater than about 15 amino acid residues, more preferably no greater

than about ten amino acid residues and most preferably no greater than about 5 amino acid residues.

Deletions are preferably deletions of no greater than about 3 amino acid residues in total (either consecutive or non-consecutive residues), more deletions preferably of 2

5 amino acids, most preferably deletions of single amino acids residues. Generally, deletions will be of amino acid residues corresponding to the "X" residues of the enhancer peptide consensus sequences.

Enhancer peptide sequences of the invention also comprise the particular enhancer peptide sequences depicted in FIGS. 2, 13 and Table 1 exhibiting one, two or three non-conservative amino acid substitutions, with two such substitutions being preferred and one such substitution being most preferred. "Non conservative" substitutions refer to substitutions with amino acid residues of dissimilar charge, size, and/or hydrophobicity/ hydrophilicity characteristics from the amino acid residue being replaced. Such amino acid characteristics are well known to those of skill in the art.

In addition, the amino acid substitutions need not be, and in certain embodiments preferably are not, restricted to the genetically encoded amino acids. Indeed, the peptides may contain genetically non-encoded amino acids. Thus, in addition to the naturally occurring genetically encoded amino acids, amino acid residues in the peptides may be substituted with naturally occurring non-encoded amino acids and synthetic amino acids.

Certain commonly encountered amino acids which provide useful substitutions include, but are not limited to,

β-alanine (β-Ala) and other omega-amino acids such as

3-aminopropionic acid, 2,3-diaminopropionic acid (Dpr),

4-aminobutyric acid and so forth; α-aminoisobutyric acid

(Aib); ε-aminohexanoic acid (Aha); δ-aminovaleric acid (Ava);

N-methylglycine or sarcosine (MeGly); ornithine (Orn);

citrulline (Cit); t-butylalanine (t-BuA); t-butylglycine

(t-BuG); N-methylisoleucine (MeIle); phenylglycine (Phg);

cyclohexylalanine (Cha); norleucine (Nle); naphthylalanine

(Nal); 4-chlorophenylalanine (Phe(4-Cl));
2-fluorophenylalanine (Phe(2-F)); 3-fluorophenylalanine
(Phe(3-F)); 4-fluorophenylalanine (Phe(4-F)); penicillamine
(Pen); 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid
(Tic); β-2-thienylalanine (Thi); methionine sulfoxide (MSO);
homoarginine (hArg); N-acetyl lysine (AcLys); 2,4diaminobutyric acid (Dbu); 2,3-diaminobutyric acid (Dab);
p-aminophenylalanine (Phe(pNH₂)); N-methyl valine (MeVal);
homocysteine (hCys), homophenylalanine (hPhe) and homoserine
(hSer); hydroxyproline (Hyp), homoproline (hPro), Nmethylated amino acids and peptoids (N-substituted glycines).

While in most instances, the amino acids of the peptide will be substituted with L-enantiomeric amino acids, the substitutions are not limited to L-enantiomeric amino acids. Thus, also included in the definition of "mutated" or "altered" forms are those situations where an L-amino acid is replaced with an identical D-amino acid (e.g., L-Arg - D-Arg) or with a D-amino acid of the same category or subcategory (e.g., L-Arg - D-Lys), and vice versa.

It is to be understood that the present invention also contemplates peptide analogues wherein one or more amide linkage is optionally replaced with a linkage other than amide, preferably a substituted amide or an isostere of amide. Thus, while the amino acid residues within peptides are generally described in terms of amino acids, and preferred embodiments of the invention are exemplified by way of peptides, one having skill in the art will recognize that in embodiments having non-amide linkages, the term "amino acid" or "residue" as used herein refers to other bifunctional moieties bearing groups similar in structure to the side chains of the amino acids. In addition the amino acid residues may be blocked or unblocked.

Additionally, one or more amide linkages can be replaced with peptidomimetic or amide mimetic moieties which do not

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significantly interfere with the structure or activity of the peptides. Suitable amide mimetic moieties are described, for example, in Olson et al., 1993, J. Med. Chem. 36:3049.

Enhancer peptide sequences can be used to enhance the pharmacokinetic properties of the core polypeptide as either 5 N-terminal, C-terminal, or - and C-terminal additions. it is preferable for the enhancer peptide sequences to be utilized in a pairwise fashion, that is, preferably hybrid polypeptides comprise an enhancer peptide sequence at both the amino- and carboxy-termini, hybrid polypeptides can also comprise a single enhancer peptide, said peptide present at 10 either the amino- or carboxy- terminus of the hybrid polypeptide. Further, the enhancer peptides can be used in either forward or reverse orientation, or in any possible combination, linked to a core polypeptide. It is noted that any of the enhancer peptides can be introduced at either the N-terminus or the C-terminus of the core polypeptide. 15 further, multiple enhancer peptide sequences can be introduced to the N-, C-, or - and C-terminal positions of the hybrid polypeptides. Multiple enhancer peptide sequences can be linked directly one to another via the same sorts of linkages as used to link an enhancer peptide sequence to the core polypeptide (see below). In addition, an intervening 20 amino acid sequence of the same sort as described below can also be present between one or more of the multiple enhancer peptide sequences. Multiple enhancer peptide sequences will typically contain from 2 to about 10 individual enhancer

25 It is understood that the core polypeptide is generally linked to the enhancer peptides via a peptide amide linkage, although linkages other than amide linkages can be utilized to join the enhancer peptide sequences to the core polypeptides. Such linkages are well known to those of skill in the art and include, for example, any carbon-carbon, ester or chemical bond that functions to link the enhancer peptide sequences of the invention to a core peptide.

peptide sequences (of the same or different amino acid sequence), with about 2 to about 4 being preferred.

Typically, an enhancer peptide sequence is linked directly to a core polypeptide. An enhancer peptide sequence can also be attached to an intervening amino acid sequence present between the enhancer peptide sequence and the core polypeptide. The intervening amino acid sequence can typically range in size from about 1 to about 50 amino acid residues in length, with about 1 to about 10 residues in length being preferred. The same sorts of linkages described for linking the enhancer peptide to the core polypeptide can be used to link the enhancer peptide to the intervening peptide.

As discussed for enhancer peptide sequences, above, core and intervening amino acid sequences need not be restricted to the genetically encoded amino acids, but can comprise any of the amino acid and linkage modifications described above.

The amino- and/or carboxy-termini of the resulting hybrid polypeptide can comprise an amino group (-NH2) or a 15 carboxy (-COOH) group, respectively. Alternatively, the hybrid polypeptide amino-terminus may, for example, represent a hydrophobic group, including but not limited to carbobenzyl, dansyl, t-butoxycarbonyl, decanoyl, napthoyl or other carbohydrate group; an acetyl group; 9fluorenylmethoxy-carbonyl (FMOC) group; or a modified, non-20 naturally occurring amino acid residue. Alternatively, the hybrid polypeptide carboxy-terminus can, for example, represent an amido group; a t-butoxycarbonyl group; or a modified non-naturally occurring amino acid residue. As a non-limiting example, the amino- and/or carboxy-termini of the resulting hybrid polypeptide can comprise any of the 25 amino- and/or carboxy-terminal modifications depicted in the peptides shown in FIG. 13 or Table 2, below.

Typically, a hybrid polypeptide comprises an amino acid sequence that is a non-naturally occurring amino acid sequence. That is, typically, the amino acid sequence of a hybrid polypeptide, does not consist solely of the amino acid sequence of a fragment of an endogenous, naturally occurring polypeptide. In addition, a hybrid polypeptide is not

intended to consist solely of a full-length, naturally occurring polypeptide.

Core polypeptides can comprise any polypeptide which may be introduced into a living system, for example, any polypeptide that can function as a pharmacologically useful polypeptide. Such core polypeptides can, for example, be useful for the treatment or prevention of disease, or for use in diagnostic or prognostic methods, including in vivo imaging methods. The lower size limit of a core polypeptide is typically about 4-6 amino acid residues. theoretically, no core polypeptide upper size limit and, as 10 such a core polypeptide can comprise any naturally occurring polypeptide or fragment thereof, or any modified or synthetic polypeptide. Typically, however, a core polypeptide ranges from about 4-6 amino acids to about 494-500 amino acids, with about 4 to about 94-100 amino acid residues being preferred and about 4 to about 34-40 amino acid residues being most 15 preferred.

Examples of possible core polypeptides, provided solely as example and not by way of limitation, include, but are not limited to, growth factors, cytokines, therapeutic polypeptides, hormones, e.g., insulin, and peptide fragments of hormones, inhibitors or enhancers of cytokines, peptide growth and differentiation factors, interleukins, chemokines, interferons, colony stimulating factors, angiogenic factors, receptor ligands, agonists, antagonists or inverse agonists, peptide targeting agents such as imaging agents or cytotoxic targeting agents, and extracellular matrix proteins such as collagen, laminin, fibronectin and integrin to name a few.

25 In addition, possible core polypeptides may include viral or

In addition, possible core polypeptides may include viral or bacterial polypeptides that may function either directly or indirectly as immunogens or antigens, and thus may be useful in the treatment or prevention of pathological disease.

Representative examples of hybrid polypeptides which comprise core polypeptides derived from viral protein sequences are shown in FIG. 13, wherein the core polypeptide sequences are shaded. Core polypeptides also include, but

are not limited to, the polypeptides disclosed in U.S. Patent No. 5,464,933, U.S. Patent No. 5,656,480 and WO 96/19495, each of which is incorporated herein by reference in its entirety.

Core polypeptide sequences can further include, but are not limited to the polypeptide sequences depicted in Table 2, below. It is noted that the peptides listed in Table 2 include hybrid polypeptides in addition to core polypeptides. The sequence of the hybrid polypeptides will be apparent, however, in light of the terminal enhancer peptide sequences present as part of the hybrid polypeptides.

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TABLE 2 :.. No. Sequence GROLDARILAYERYLKDQ 2 **NUMBER OF THE PROPERTY OF THE** 3 **NEOELLELDKWASLWKWF** YTELIKSLIEESONOOEK 4 5 Ac-YWGIKQLQARILAVERYLKDQQLLGIWG-NH2 **OHLLOLTYWGIKOLOARILAVERYLKDO** 6 LRAIEAQQHLLQLTVWGIKQLQARILAV 7 VQQQNNLLARIEAQQHLLQLTVWGIKQL 8 ROLLSGIVQQQNNLLRAIEAQQHLLQLT 10 MTLTVQARQLLEGIVQQQNNLLRAIEAQ VVSLENGVSVLTEKVLDLKNYIDKQLL 12 LLSTNKAVVSLENGVSVLTSKVLDLKNY 13 AC-VILHLEGEVNKIKSALLSTNKAVVSLSNG-NH2 15 AC-LLETHKAVVSLENGVSVLTSKVLDLKNY-NH2 19 Ac-YTSLIKSLIEESQNQQEKNEQELLELDKWASLWNWF-NH2 20 21 AC-NNLLRAIEAQQHLLQLTVWGIKQLQARILAVERYLKDQ-NH2 22 AC-TELSNIKENKCNGTDAKVKLIKQELDKYKNAVTELQLLMQST-NH2 AC-IELSNIKENKCNGTDAKVKLIKQELDKY-NH2 23 Ac-ENKCNGTDAKVKLIKQELDKYKNAYTEL-NH2 21 25 Ac-DAKYKLIKQELDKYKNAVTELQLLMQST-NH2 Ac-CHGTDAKVKLIKQELDKYKNAVTELQLL-NH2 26 AC-SNIKENKCHGTDAKVKLIKQELDKYKNAVTELQLL-NH2 AC-ASGYAVSKYLHLEGEVNIKIKSALLSTNIKAVVSLSNGV-NH2 28 29 AC-GOVAVSKYLHILEGEVNKIKSALLETNKAVVSLSNG-NH2 30 AC-VILHLEGEVNIKIKSALLSTHKAVVSLSNGVSVLTSK-RIH2 AC-ARKLORMKOLEDKVEELLSKNYHYLENEVARLKKLV-NH2 21 AC-RIKOLEDKVEELLSKNYHYLENEVARLKKLVGER-NH2 Ac-VOQONNILI RATEADOHILLOLTVINGIKOLANII2 23 24 AC-LRAIEAQQHILLQLTVVVGIKQLQARILAV-NH2 35 Ac-QHILLQLTVWGIKQLQARILAVERYLKDQ-KH2 36 AC-ROLLEGIVOQONNILLRAIEAQQHILLQLT-NH2 37 AC-MILTVQARQLLSGIVQQQNINLLRAIEAQ-NH2 38 AC-AKQARSDIEKLKEAIRDTNKAVQSVQSS-NH2 29 Ac-AAVALVEAKQARSDIEKLKEAIRDTNKAVQSVQSS-KH2 Ac-AKQARSDIEKLKEAIRDTHKAVQSVQSSIGNILIVA-NH2 40 41 AO-GTIALGYATSAQITAAYALYEAKDARSD-KH2 49 AC-ATSAQITAAVALVEAKQARSDIEKLKEA-IIH2 AC-AAVALVEAKQARSDIEKLKEAIRDTNKA-NH2 44 Ac-IEKLKEAIROTNIKAVQSVQSSIGNILIVA-NIH2 45 Ac-IRDTNIKAVQSVQSSIGNLIVAIKSVQDY-KIHZ Ac-AVQSVQSSIGRILIVARGSVQDYVNIKEIV-HIH2 47 Ac-QARQLLEGTVQQQHHLLRAIEAQQHILLQLTVWGIKQLARILAVERYLKDQ-HH2 48 Ac-QAROLLEGIVOQONNILIRAIEADOHILIO-NH2 -49 Ac-ATYMENDREINNYTSLIGSLIEESQHQQEKNEQELLELDKWASLWNWF-KH2 60 AC-WINEWDREINNYTSLIGSLIEESONOOEKNEOFILE-KIHZ 61 AC-MINTELIGSLIEES CHOOLEKHEOELLE-KHZ 62 AC-INNYTSLIGSLIEESONQOEKNEGELLELDKWASL-NH2 Ac-ENDRENNYTELIGSLEESCHOOFIGEOEGGC-KH2 A - OSHTILLAGVOCCOCLIDAVKROCELLRAHEZ A - HONOTHOEMERKYDFLEENTALLEEACICCERRINTELDRINSWD-HIRZ 24 2

T No.	Sequence	* , * t .
64	Ac-WOENERKVOFLEERITALLEEADIQUEKRIPE	
67 ·	A6-VOFLEERITALLEEAQIQQERRINYELQK-48H2	
68	AO-ITALLEEAQKQQEKKBIYELQKLHSWDVF-HIH2	
69	A-SSESFTLLEOWNWKLOLAEOWLEONEKHYLEDIS-HHZ	
; 60	Ac-DKWASLWHWF-HH2	
61	AC-NEGELLELDKWASLWHWF-NH2	
62	AC-EKNEGELLELDKWASLWNWF-NH2	
63	ACHQQEKNEQELLELDKWASLWNWF-NH2	
64	AC-ESQNQQEKNEQELLELDKWASLWNWF-NH2	
65	AC-LIHSLIEESQHQQEKNEQELLELDKWASLWAWF-NH2	
66	ACHIDQKKLMSHNYQIYRQQSYSIMSIIKEEHHZ	
67	Ac-DEFDASISQVNEKINQSLAFIRKSDELL-NH2	
68	Ac-VSKGYSALRTGWYTSVITIELSNIKEN-NH2	
. 69	Ac-Welengvevltekvldlknyidkoll-nih2	
70	Ac-vnikiksallstnikavvslengvsvltsk-nih2	
71	AC-PUNFYDPLYFPSDEFDASISQYNEKINQSLAFIR-NH2	
72	AC-NL-YYAQLQFTYDTLRGYINRALAQIAEA-NH2	
73	AC-LNOVOLTETLERYQORLNTYALVSKOASYRS-NH2	
74	Ac-ELLVLKKAQLNRHSYLKDSDFLDAALD-HH2	
75	AC-LAEAGEESVTEDTEREDTEEEREDEEE-NH2	
76	Ac-ALLAEAGEESVTEDTEREDTEEEREDEEEENEART-NH2	
77	Ac-ETERSYDLYAALLAEAGEESYTEDTEREDTEEERE-NH2	
78	Ac-EESVTEDTEREDTEEEREDEEEENEART-NH2	
79	AO-YOLVAALLAEAGEESYTEDTEREDTEEE-NH2	•
80	AC-HISETERSYDLYAALLAEAGEESYTE-NH2	
81	Ac-DISYAQLQFTYDVLKDYINDALRNIINDA-NH2	•
82	Ac-Shvfskdeikireynsqkohirtlsakvndh-ki+2	7
63	BIORIN-YTELLIHELIEESQHQQEKNEQELLELDKWASLWNWF-NH2	
84	DIG-YTSLIHSLIEESCHQCEKNECHELELDKWASLWHWF-KH2	
85	BIOGIN-KNILL RAIEAQQHILLOLTVWGIKQLQARILAYERYLKDQ-KH2	•
■6	DIG-HINLLRAIEAQCHILLOLTVWGIKOLOARILAVERYLKDQ-HIH2	
67	AC-VILHOLNIQLKQYLETQERILAGNRIAARQLLQIWKDVA-NH2	
88	Ac-LWHECLLHTAGRAGLOLQLHOALAVREKYLIRYDIQK-HH2	
89	ACLIENTESTWEQSKELWEQGEISIQHILHKSALQEYWHH2	
90 91	AO-LENLLQISKKISDEWLEALEIEHEKWKILTQWQSYEQF-NH2	
82	AOKLEALEGKLEALEGKLEALEGKLEALEGKANN2	
93	AO EL MARTI FORMA A FORMA MARTINA MART	
84	AO-ELKAKELEGEGLAEGEEALKGLEKAAKLEGLELLK-NH2 AO-WEAAAREAAAREAAAREAARA-NH2	
95	Aoytslikslieesqikqqeiqreqelleldkwaslwaaf-kik2	
96	AOYTELHSLIFESONOQEINEGELLELDKWASLANWF-4612	
87	AC-YTELEHELEEEOHOOEHOOELLELDKWASLWKWF-RH2	
88	ACYTELHELEESOHQOEKKEGELLOLDKWASLWHWF-NH2	
99	AC-YTELEHELIFESONQQERNQQELLQLDKWASLWMWF-NH2	
100	Ac-RAIKOLEDKVEELLEKKYHLENEVARLKKLYGER-HIHZ	
. 101	Ac-QQLLQLTVWGKQLQARILAVERYLKHQ-KH2	
102	Achierelleedkwaelhmmi-nih2	
103	AC-YTSLIQSLIFEEQHQQERGEQELLELDKWASLWKWF-4812	
104	AO-INITYDPLYFPSDEFDASISONNEKINOSLAFIRIKAIH2	
105	ACHETOPLYITEDE DUSSONESSICISTICIPATE THE	

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1101	Sequence		-
106	Ac-HETOPLYFFEDEFDASISQVNEKHQSLAFIRKSD-HH2		
107	Ac-FYDPLYFP6DEFDASISQVNEIGHQSLAFIRKSDE-KH2		
108	Ac-ydplyfpsdefdasisgynekingslafirksdelakh2		
109	Ac-dpl.vfpsdefdasisqvneringslafirksdellank2		
110	Ac-PLYFPSDEFDASISQYNEKINQSLAFIRKSDELLH-KIH2		
111	Ac-Lyfpsdefdasisqynekinqslafirksdellhin-nih2		
112	Ac-VFPSDEFDASISQVNEKINQSLAFIRKSDELLHNV-KH2		
113	AC-FPSDEFDASISQVNEKINQSLAFIRKSDELLHKVN+KH2		
114	Ac-PSDEFDASISQVNEKINQSLAFIRKSDELLHNYNA-NH2		
115	Ac-SDEFDASISQVNEKINQSLAFIRKSDELLHINVKAG-KH2		
116	Ac-DEFDASISQVNEKINQSLAFIRKSDELLHNVNAGK-NH2		
117	Ac-EFDASISQVNEKINQSLAFIRKSDELLHNVNAGKS-NH2		
118	Ac-FDASISQVNEKINQSLAFIRKEDELLHNVNAGKST-NH2		
119	Ac-Dasisqvhekingslafirksdellhinvnagkstt-kih2		
120	Ac-Asgvavskylhilegevnkiksallstnkavvslsn-nh2		
121	Ac-SGVAVSKVLHILEGEVNKIKSALLSTNKAVVSLENG-NH2		
122	Ac-GVAVSKVLHLEGEVNKKKSALLETNKAVVSLENGV-KH2		
123	Ac-VAVSKVLHLEGEVNKIKSALLETNKAVVSLENGVS-NH2		
124	Ac-Avskylhlegevnkiksallstnkavyslsngvsv-hh2		
125	Ac-VSKVLHLEGEVNKIKSALLSTNKAVVSLSNGVSVL-NH2		
126	AO-SKYLHILEGEVNKIKSALLETNKAVVSLENGVSVLT-NH2		•
127	Ac-KVLHLEGEVNICKSALLSTNKAVVSLSHGVSVLTS-HH2		
128	Ac-VLHLEGEVNICKSALLETNIKAVVSLENGVSVLTEK-NH2		
129	Ac-LHILEGEVNICKSALLSTNKAVVSLSNGVSVLTSKY-NH2		
130	Ac-HILEGEVNKIKSALLSTNKAVVSLSHGVSVLTSKVL-NH2		
. 131	Ac-legevnicksalletnikavvelengvevltekvld-nih2		•
132	Ac-EGEVNKIKSALLETHKAVVSLSHGVSVLTSKVLDL-NH2		*
133	AO-GEVNKIKSALLETNIKAVVELEHGVEVLTEKVLDLK-NH2		
134	AO-EVIKKIKSALLETNIKAVVSLEHGVSVLTSKVLDLIGH-NH2		
135	Ac-Mikiksalletnikavvslengvsvltskvldlikhy-kh2		
136	Ac-HRIKSALLETRIKAVYSLEHGYSVLTEKVLDLKHYTHH12		•
137	AC-KIKEALLETHIKAVVELEHGVEVLTEKVLDLIKHYID-KH2		
138	AC-KEALLETHKAVVELEHGYEVLTEKVLDLKHYIDK+HH2		•
139	Ac-Keallethkavvelehgvevltekvldlirnyidkq-hi+12		
140	Ao-EALLETRIKAVVELENGVEVLTEKVLDLIGNYIDKOLAGH2		
141	ACALLETNIKAVVSLEHGVSVLTSKVLDLKHYTDKOLLAH2		
142	AO-YTEVITTELENIKENKCHGTDAKVALIKQELDKYK-HIH2		
143 144	AG-TEVITTELEKIKENKCHGTDAKYKILEKCIELDKYKKHRILE		
145	A-SYTTELSKIKERIKCHGTDAKYKLIKCELDKYKNA-KK12		
146	Ac-VITTELSKIKENKCHGTDAKVKLIKQELDKYKNAV-NH2		
147	Ac-THE SUNCENCROTTO A SECTION OF THE		
948	AO-TIELSKUKENKCHGTDAKYKLIKOELDKYKNAVTE-KIRIZ AO-KELSKUKENKCHGTDAKYKLIKOELDKYKNAVTE-KIRIZ		
149	A-ELSHIKENKCHGTDAKVKLIKQELDKYKNAYTELQ+012		
160			
161	A-LINGENCONGTDAKVIGLIKOELDKYKNAVTELQL-KH2		
162	Ao-SHECERICCHGTDAKVKLEGGELDKYKNAVTELGLLANH2 Ao-RECERICCHGTDAKVKLEGGELDKYKNAVTELGLLANH2		
163	A-4999CHGTDAKVKLIKQELDKYKRIAVTELQLLIKQ4612		
164	Ac-KENOCKGTDAKYNG KOELDKYNGKYTELOLL 1102-1612		
€66	ACERCHITTARVIOLICOELDICICIAVIEDALMOST-1812		
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No.	Sequence	•	
104			-
157	A-LLONFESTWEGSKELWELGESIGNLINGALGEYWH-KIH2		
168	Ao-Alávatsaoitaavalveakoarsdieklkeard-kki Ao-Lävatsaoitaavalveakoarsdieklkeardt-kki		
169	Ac-GYATSAGITAAYALYEAKQARSDIEKLKEARDTH4H2		
160			
161	AO-VATSAGITAAVALVEAKQARSDIEKLKIEAIRIDTRIKKHIZ		
162	AO-ATSAQITAAVALVEAKQARSDIEKLKEAIROTRIKA-NIH2		
163	Ac-TSAQITAAVALVEAKQARSDIEKLKEAIRDTNIKAV-KH2		
164	A-SACITAAVALVEAKOARSDIEKLIKEAIROTTIKKAVQ-NIH2		-
165	Ac-ACITAAVALVEAKOARSDIEKLKEAIRDTNKAVOS-NH2		
166	AO-QITAAVALVEAKQARSDIEKLKEAIRDTNIKAVQSV-NH2 AO-ITAAVALVEAKQARSDIEKLKEAIRDTNIKAVQSVQ-NH2		
167	AC-TAAVALVEAKQARSDIEKLKEAIRDTNIKAVQSVQS-NH2		
168	Ao-AAVALVEAKQARSDIEKLKEAIRDTNKAVQSVQS-KH2		
169	Ac-AVALVEAKQARSDIEKLKEAIRDTNKAVQSVQSS-NH2		
170	Ac-VALVEAKQARSDIEKLKEAIRDTNKAVQSVQSSIG-NH2		
171	Ac-Alveakoarsdierlikeairdtrikavosvossigh-hih2		
172	Ac-Lyeakoarsdieklkeairdthkayosyosskrhaki2		
173	Ac-VEAKQARSDIEKLKEAIRDTHKAYQSYQSSIGNIL-KIH2		
174	Ac-EakQarsdieklkeairdtnikavqsvqssignily-nihz		
176	Ac-Koarsdieklkeairdthikavosvossignlivalhih2		
176	Ao-Qarsdieklkeairdthkavqsvqssignilvaikabl2		
177	Ac-Arsdieklkeairdthkavosvossigklivaiks-kit2		
178	Ao-RSDIEKLKEAIRDTKKAVOSVOSSIGKLIVAIKSV-KIHZ	-	
179	AG-SDIEKLKEAIRDTHIKAYQSYQSSIGNLIVAIKSYQ-HH2		<i>;</i>
180	Ac-DIEKLKEAIRDTNKAVQSVQSSKGKLIVAIKSVQD-KH2		
181	Ac-HEICLKEARDTHIKAVQSVQSSIGNLIVAIKSVQDY-NH2		
182	Ao-EKILKEAKROTIKKAVQSVQSSKGKILVAKKSVQDYV-KH2		,
183	AO-KILKEAIRDTKKAVQSVQSSKGHLIVAIKSVQDYVH+HH2		.· '
184	AC-LICEARDTHIKAVQSVQSSKGHLIVAIKSVQDYVNKANI2		
185	AO-KEARDTHKAYQSYQSSIGHLIYAKGYQDYYNKGHIHZ		
186	AO-EAIRDTNIKAVQSVQSSIGHLIVAIKEVQDYVNIKEHIHZ		
187	Ao-AIRDTHKAVQSVQSSIGHLIVAIKSVQDYVNKEIV-HH2		
188	Ac-IRDTNKAYQSYQSSIGKLIVARQSYQDYYNKEIV-4KHZ		
189	AC-YTPHOTILNINSVALDPIDISIELNIKAKSDLEESKE-NH2		•
190	Ac-TPHOITLINISVALDPIDISTELNIKAKSDLEESKEW-NH2	•	
191	AO-PHOTTLHRSVALDPIDISIELHKAKSDLEESKEWI-HIHZ		
192	Ac-KOTTLKKSVALDPIDISTELKKAKSDLEESKEWIR-KH2		
193	Ac-DITTANSVALDPIDISEELNIKAKSDLEESKEWIRR-NH2		
104	AO-ITLINISVALDPIDISTELNIKANSDLEESKEWRRS-NHZ		
185	AC-TLINSVALDPIDISTELKKAKSDLEESKENTRRSN-HILL		
196	A-LINSVALDPIDISELIKAKSDLEESKEWERESHQ-HH2		
197 198	Ac-MNSVALDPIOISIELNKAKSDLEESKEH/IRRSKOK-NH2		
200	Ac-MSYALDPIDISIELAKAKSDLEESKEWIRRSKOKLAH2		
201	Ao-VALDPIDISTELNIKAKSDLEESKEWIRRSHCKLDS-NH2		
201	A-ALDPIDISTELVKAKSDLEESKEWRRSHQKLDSI-HI-12		
202	Ac-LDPIDISTELNIKAKSDLEESKEWIRRSHOKLDSIG-NI-12		
204	Ac-Prosielrkaksoleeskeykrrshokloskkhiliz Ac-Prosielrkaksoleeskeykrrshokloskkhyhliz		
205	Ao-DISTELAKAKSDLEESKENERSHOKLDSTOKWINE2		
206	A-DESELARANSOL E-SK-WERT-SKORDSGRIMO-WILL		
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T No.	Commen		
	Sequence Company of the Company of t		-
207	Ac-ISIELHKAKSDLEESKEHRRSHORLDSIGHWHQS-4742	·	
206	AO-SIELHKAKSDLEESKEMRRSHOKLDSKINWHQSS-NH2		
209	AO-RELNKAKSDLEESKEHIRRSNOKLDSIGNYHOSST-NIA		
210	AO-ELNIKAKSDLEESKEWIRRSHQKLDSKHWHQSSTT-NH2		
211	AO-ELRALRGELRALRGELRALRGELRALRGEALRGK-NH2		
212	AC-YTELIHSLIEESQNQQQKKEQELLELDKWASLWKWF-KH2	•	
213	AC-YTSLIHSLIEESQNQQEKNEQELLELNKWASLWNWF-NH2		
214	AC-YTSLIHSLIEQSQNQQEKNEQELLELDKWASLWNWF-NH2		•
215	AC-YTSLIHSLIGESQNQQEKNEQFLLELDKWASLWNWF-NH2		
216	AC-YTELIHELIQQSQNQQQKNQQQLLQLNKWASLWNWF-NH2		
217	Ac-EQELLELDKWASLWNWF-NH2		
218	Ac-QELLELDKWASLWNWF-NH2		
219	AC-ELLELDKWASLWNWF-NH2		
22 0	ACLLELDKWASLWNWF-NH2	·	
· 22 1	AC-LELDKWASLWNWF-NH2		•
. 222	Ac-ELDKWASLWNWF-NH2	•	
· 22 6	AC-WASLWHWF-HH2		
- 22 7	AC-ASLWNWF-NH2		
229	AC-YTSLIHSLIEESQNQQEKNEGELLELDKWASLANAA-NH2		
230	AC-YTSLIHSLIEESQNQQEKNERQLLELDKWASLWNWF-KH2		
-231	AC-YTSLIQSLIFESQNQQEKHQQELLELDKWASLWNWF-NH2		
234	AC-EAAAREAAAREAAARLELDKWASLWHWF-NH2		
· 23 6	Ac-PSLRDPISAEISIQALSYALGGDINKYLEKLGYSG-HH2		,
237	Ao-SLRDPISAEISIQALEYALGGDINKVLEKLGYSGG-KH2		- 4
- 238	Ao-LRDPISAEISIQALSYALGGDINKVLEKLGYSGGD-NH2		•
239	AO-ROPISAEISKOALEYALGGDINKYLEKLGYEGGDL-KH2		
- 240	AC-OPISAEISIQALEYALGGDINKVLEKLGYEGGDILLA(H2		•
-241	AO-PISAEISIQALSYALGGDIKKVLEKLGYSGGDLLG-KH2		<i>:</i>
. 242	AO-ISAEISIQALEYALGGONKKYLEKLGYEGGOLLGHNH2		
243	Ac-SAEISIQALSYALGGDIRKVLEKLGYSGGDLLGIL-KIH2		
244	A-AESIQALEYALGGDIRKVLEKLGYSGGDLLGILE-KH2		
245 246	AO-EISIQALSYALGGDINKVLERLGYSGGDLLGILES-HH2		
247	A-SIGNLEYALGGDRIKVLEKLGYEGGDLLGREER-KH2		
248	Ao-Sigaleyalggdirikvleklgyeggdilgilesrg-rihz Ao-Kqaleyalggdirikvleklgyeggdilgilesrg-rihz		
249	Ac-QALSYALGGDINKVI ERI GYSGGDLL GII FRRGIKAHI?		
260	AO-ALEYALGGDINKYLEKLGYEGGDLLGILEERGIKA-HH2		
251	Ac-LSYALGGDRIKVLEKLGYEGGDLLGILESRGIKAR-HH2		
252	AO-PDAYYLHRIDLGPPISLERLDYGTNLGKAIAKLED-1612		
253	Ac-DAVYLHRIDLGPPISLERLDYGTNLGNAIAKLEDA-NH2		
254	Ac-AVYLHRIDLGPPISLERLDVGTHLGHAIAKLEDAK-HH2		
265	Ac-Wilhridusppislerldvgthlghalakledake-kih2		
256	AO-YLHRIDLGPPISLERLDVGTKLGNAUAKLEDAKEL-NH2		
257	Ac-LHRIDLGPPISLERLDVGTRILGNAIAKLEDAKELL-NH2		
258	Ac-HRIDLGPPISLERLDVGTHLGNAJAKLEDAKELLE-NH2		
259	Ac-RIDLGPPISLERLDVGTKLGNAIAKLEDAKELLES-NIH2		
260	Ac-IDLGPPISLERLDVGTHLGHAIAKLEDAKELLESS-1012		
201	Ac-DLGPPISLERLDVGTHLGHAIAKILEDAKELLESSD-KIIZ		
262	Actoppisteredvotneonalakiedakielessoojihiz		
263	As GPPISLERLDYGTRICKALIKE EDAYED SEEDO MID		
	A. A. A.		•

864 A-PESLERIDYOTTI GRANAKI EDAREL LESSOCIA-RIC? 865 A-PESLERIDYOTTI GRANAKI EDAREL LESSOCIA-RIC? 866 A-PESLERIDYOTTI GRANAKI EDAREL LESSOCIA-RIC? 866 A-PESLERIDYOTTI GRANAKI EDAREL LESSOCIA-RIC? 867 A-SERIDYOTTI GRANAKI EDAREL LESSOCIA-RIC? 868 A-LERIDYOTTI GRANAKI EDAREL LESSOCIA-RICR 869 A-LERIDYOTTI GRANAKI EDAREL LESSOCIA-RICR 869 A-LERIDYOTTI GRANAKI ESSOCIA-RICR 860 A-LERIDYOTTI GRANAKI ESSOCIA-RICR 860 A-LERIDYOTTI GRANAKI ESSOCIA-RICR 871 A-LERIDYAKI GRANAF-RICR 872 A-LERIDYAKI GRANAF-RICR 873 A-LERIDYAKI GRANAF-RICR 874 A-BELGINYAKI GRANAF-RICR 875 A-BELGINYAKI GRANAF-RICR 876 A-BELGINYAKI GRANAF-RICR 876 A-BELGINYAKI GRANAF-RICR 877 A-BELGINYAKI GRENIK GRANAKI GRANAF-RICR 877 A-BELGINYAKI GRENIK GRANAKI GRANAF-RICR 878 A-BELGINYAKI GRENIK GRANAKI GRANAF-RICR 879 A-BELGINYAKI GRENIK GRANAKI GRANAF-RICR 870 A-BELGINYAKI GRENIK GRANAKI GRANAF-RICR 870 A-BELGINYAKI GRENIK GRANAKI GRANAF-RICR 870 A-BELGINYAKI GRANAKI GRENIK GRANAF-RICR 870 A-BELGINYAKI GRANAKI GRANAF-RICR 870 A-BELGINYAKI GRANAKI GRANAKI GRANAF-RICR 870 A-BELGINYAKI GRANAKI GRANAF-RICR 870 A-BELGINYAKI GRANAKI GRANAF-RICR 870 A-VIGIN GISTEL GRANAKI GRANAF-RICR 870 A-VIGIN GISTEL GRANAKI GRANAF-RICR 870 A-SCHYTORILDISTEL GRANAKI GRANAF-RICR 870 A-SCHYTORILDISTEL GRANAKI GRANAF-RICR 870 A-SCHYTORILDISTEL GRANAKI GRANAF-RICR 870 A-SCHYTORILDISTEL GRANAKI GRANAF-RICR 870 A-SCHOOLDISTEL GRANAF-RICR HARLER 871 A-SCHOOLDISTEL GRANAF-RICR HARLER 872 A-SCHOOLDISTEL GRANAF-RICR HARLER 873 A-SCHOOLDISTEL GRANAF-RICR HARLER 874 A-SCHOOLDISTEL GRANAF-RICR HARLER 875 A-SCHOOLDISTEL GRANAF-RICR	T.	•	3 **	4.
APPELER DYGITE GRANAK ENAKEL ESSOCI RANGE APPELER DYGITE GRANAK ENAKEL ESSOCI RANGEN APPELER DYGITE GRANAK ENAKEL ESSOCI RANGEN APPELER DYGITE GRANAK ENAKER APPELER DYGITE GRANAK ENAKER ENAKER DYGITE DYGITE DYGITE DYGITE DYGITE DYGITE GRANAK ENAKER ENAKER DYGITE DYGIT DYGITE DYGIT DYGITE DYG	Ho.	Sequence		
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AGERLDYGTREGNAUNG EDAYGE LESSDOIL RSMAHR ALERIDYGTREGNAUNG EDAYGE LESSDOIL RSMAHR ALERIDYGTREGNAUNG SHIRE ALERIDYGNASLAMAPHR ALERIDYGNASLAMAPH	265	AO-PISLERLDYGTNILGNAIAKLEDAKELLEGSDOILR-NH2	·	
AC-LERICHGENSHUR AC-LUR AC-LERICHGENSHUR AC-LUR AC	266	Ac-ISLERI, DYGTNI, GNAIAKI EDAKELLESSDQIRS-NH2		
AGENRIESKORDSHINE AGELDKWASLANAFARIR ACHEDKWASLANAFARIR ACHEDKWASLANALDKLEESKIKLDKWAVATTERARIR ACHEDSTELGKWARSISHALDKLEESKIKLDKWAVATRIR ACHIDISTELGKWARSISHALDKLEESKIKLDKWAVARIR ACHEDSTELGKWARSISHALDKLEESKIKLDKWAVARIR ACHEDSTELGKWARSISHALDKLEESKIKLDKWAVARIR ACHTORILDSTELGKWARSISHALDKLEESKIKLDKWAVARIR ACHTORILDSTELGKWARSISHALDKLEESKIKLDKWAVARIR ACHTORILDSTELGKWARSISHALDKLEESKIKLDKWAVARIR ACHTORILDSTELGKWARSISHALDKLEESKIKLDKWARIR ACHTORILDSTELGKWARSISHALDKLEESKIKLDKWARIR ACHTORILDSTELGKWARSISHALDKLEESKIKLDKWARIR ACHTORILDSTELGKWARSISHALDKLEESKIKLDKWARIR ACHTORILDSTELGKWARSISHALDKLEESKIKLDKWARIR ACHTORILDSTELGKWARSISHALDKLEESKIKLDKWARIR ACHTORILDSTELGKWARSISHALDKLEESKIKLDKWARIR ACHDSQWYTGRLDSTELGKWARSISHALDKLEESKIKLDKWARIR ACHDSQWYTGRLDSTELGKWARSISHALDKLEESKIKLDKWARIR ACHDSQWYTGRLDSTELGKWARSISHALDKLEESKIR ACHDSQWYTGRLDSTELGKWARSISHALDKLEESKIR ACHDSQWYTGRLDSTELGKWARSISHALDKLEESKIR ACHTORICSBJOCKYTGRLDSTELGKWARSISHALDKLEEKIR ACHTORICSBJOCKYTGRLDSTELGKWARSISHALDKLEER ACHTORICSBJOCKYTGRLDSTELGKWARSISHALDKLEER ACHTORICSBJOCKYTGRLDSTELGKWARSISHALDKARR ACHTORICSBJOC	267	Ao-SLERLDYGTHLGNAIAKLEDAKELLESSDQILRSHI-NH2		
ACLEDINASLANAFARIZ ACLEDINASLANAFARIZ ACLEDINASLANAFARIZ ACLEDINASLANAFARIZ ACLEDINASLANAFARIZ ACCEDINASSINALDILEENISLDINANACITETEARIZ ACCEDINASSINALDILEENISLDINANACITETEARIZ ACCEDINASSINALDILEENISLDINANACITETEARIZ ACCEDINASSINALDILEENISLDINANACITETEARIZ ACCEDITELGANANISSINALDILEENISLDINANACITETEARIZ ACCEDITELGANANISSINALDILEENISLDINANACITETEARIZ ACCEDITELGANANISSINALDILEENISLDINANACITETEARIZ ACCEDITELGANANISSINALDILEENISLDINANACITETEARIZ ACCEDITELGANANISSINALDILEENISLDINANACITERIZ ACCEDITELGANANISSINALDILEENISLDINANACITERIZ ACCEDITELGANANISSINALDILEENISLDINANACITERIZ ACCEDITELGANANISSINALDILEENISLDINANACITERIZ ACCEDITELGANANISSINALDILEENISLDINANACITERIZ ACCEDITELGANANISSINALDILEENISLDINANACITERIZ ACCEDITELGANANISSINALDILEENISLDINANACITERIZ ACCEDITELGANANISSINALDILEENISLDINANACITERIZ ACCEDITELGANANISSINALDILEENISLDINANACITERIZ ACCEDITELGANANISSINALDILEENISLADILEENISLDINANACITERIZ ACCEDITELGANANISSINALDILEENISLADILEENISL	268	Ac-LERLDYGTHLGNAIAKLEDAKELLESSDQILRSIKK-HH2		
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272 AC-LEDKWASLANWF-Nit2 273 AC-LEDKWASLANWF-Nit2 274 AC-LEDKWASLAWAR-Nit2 275 AC-LEDKWASLAWAR-Nit2 276 AC-LEDKWASLSWALDKLEESHSKLDKWAWKLTSTE-Nit2 277 AC-STELGKWANSLSWALDKLEESHSKLDKWAWKLTSTE-Nit2 277 AC-STELGKWANSLSWALDKLEESHSKLDKWAWKLT-Nit2 278 AC-DISTELGKWANSLSWALDKLEESHSKLDKWAWKLT-Nit2 279 AC-DISTELGKWANSLSWALDKLEESHSKLDKWAWKLT-Nit2 270 AC-LDISTELGKWANSLSWALDKLEESHSKLDKWAWKLT-Nit2 271 AC-LDISTELGKWANSLSWALDKLEESHSKLDKWAWKLT-Nit2 272 AC-TORLDISTELGKWANSLSWALDKLEESHSKLDKWAWKLT- 273 AC-GRUDISTELGKWANSLSWALDKLEESHSKLDKWANZ 274 AC-WYTGKLDISTELGKWANSLSWALDKLEESHSKLDKWANZ 275 AC-WYTGKLDISTELGKWANSLSWALDKLEESHSKLDKWANZ 276 AC-WYTGKLDISTELGKWANSLSWALDKLEESHSKLDKWANZ 277 AC-SCWYTGKLDISTELGKWANSLSWALDKLEESHSKLDKWANZ 278 AC-SCWYTGKLDISTELGKWANSLSWALDKLEESHSKLDWANZ 279 AC-SCWYTGKLDISTELGKWANSLSWALDKLEESHSKLDWANZ 270 AC-SCWYTGKLDISTELGKWANSLSWALDKLEESHSKLDWANZ 270 AC-SCWYTGKLDISTELGKWANSLSWALDKLEESHSKLDWANZ 271 AC-SCWYTGKLDISTELGKWANSLSWALDKLEESHSKLDWANZ 272 AC-SCWYTGKLDISTELGKWANSLSWALDKLEESHKWANZ 273 AC-SCWYTGKLDISTELGKWANSLSWALDKLEESHWANZ 274 AC-SCRUSTORDISTELGKWANSLSWALDKLEESHWANZ 275 AC-SCRUSTORDISTELGKWANSLSWALDKLEESHWANZ 276 AC-SCRUSTORDISTELGKWANSLSWALDKLEESHWANZ 277 AC-SCRUSTORDISTELGKWANSLSWALDKLEESHWANZ 278 AC-SCRUSTORDISTELGKWANSLSWALDKLEESHWANZ 279 AC-SCRUSTORDISTELGKWANSLSWALDKLEESHWANZ 270 AC-SCRUSTORDISTELGKWANSLSWALDKWANZ 270 AC-SCRUSTORDISTELGKWANSLSWALDKWANZ 271 AC-YCROSELDSCWYTGKLDISTELGKWANSLSWALDKWANZ 272 AC-YCROSELDSCWYTGKLDISTELGKWANSLSWALDKWANZ 273 AC-YCROSELDSCWYTGKLDISTELGKWANSLSWALDWANZ 274 AC-YCROSELDSCWYTGKLDISTELGKWANSLSWALDWANZ 275 AC-YCROSELDSCWYTGKLDISTELGKWANSLSWALDWANZ 276 AC-YCROSELDSCWYTGKLDISTELGKWANSLSWALDWANZ 277 AC-YCROSELDSCWYTGKLDISTELGKWANSLSWALDWANZ 278 AC-YCROSELDSCWYTGKLDISTELGKWANSLSWALDWANZ 279 AC-YCROSELDSCWYTGKLDISTELGKWANSLSWALDWANZ 270 AC-SCRUSTAWANZ 270 AC-SCRUSTA	270	Ac-LELDKWASLANAF-NH2		
AC-ELDKWASLYMAF-NIK 27 AC-ELDKWINSSINALDK EESINSKLDKVWYKLTSTSA-NIK 27 AC-STELGKWINSSINALDK EESINSKLDKVWYKLTSTSA-NIK 27 AC-STELGKWINSSINALDK EESINSKLDKWYKLTSTSA-NIK 27 AC-STELGKWINSSINALDK EESINSKLDKWYKLTS-NIK 27 AC-STELGKWINSSINALDK EESINSKLDKWYKLT-NIK 27 AC-DISTELGKWINSSINALDK EESINSKLDKWYKLT-NIK 28 AC-DISTELGKWINSSINALDK EESINSKLDKWYKLT-NIK 28 AC-ALDISTELGKWINSSINALDK EESINSKLDKWYKH-NIK 28 AC-ACHLDISTELGKWINSSINALDK EESINSKLDKWYKH-NIK 28 AC-YTGKLDISTELGKWINSSINALDK EESINSKLDKWYKH-NIK 28 AC-YTGKLDISTELGKWINSSINALDK EESINSKLDKWIN-NIK 28 AC-YTGKLDISTELGKWINSSINALDK EESINSKLDKWIN-NIK 28 AC-YTGKLDISTELGKWINSSINALDK EESINSKLDKWIN-NIK 28 AC-YTGKLDISTELGKWINSSINALDK EESINSKLDK-NIK 28 AC-YTGKLDISTELGKWINSSINALDK EESINSKLDK-NIK 28 AC-YTGKLDISTELGKWINSSINALDK EESINSKLDK-NIK 28 AC-GOVYTGKLDISTELGKWINSSINALDK EESINSKLDK-NIK 29 AC-DISCOVYTGKLDISTELGKWINSSINALDK EESINSKL-NIK 20 AC-DISCOVYTGKLDISTELGKWINSSINALDK EESINSKL-NIK 20 AC-DISCOVYTGKLDISTELGKWINSSINALDK EE-NIK 20 AC-BISCOVYTGKLDISTELGKWINSSINALDK EE-NIK 21 AC-GISCOSLDISTELGKWINSSINALDK EE-NIK 22 AC-SILDSCVIVTGKLDISTELGKWINSSINALDK EE-NIK 23 AC-GISCOSLDISTELGKWINSSINALDK EE-NIK 24 AC-GISCOSLDISTELGKWINSSINALDK EE-NIK 25 AC-GISCOSLDISTELGKWINSSINALDK EE-NIK 26 AC-GISCOSLDISTELGKWINSSINALDK EE-NIK 27 AC-TYCKGSLDISCOVTGKLDISTELGKWINSSINALDK EE-NIK 28 AC-GISCOSLDISCOVTGKLDISTELGKWINSSINALDK EE-NIK 29 AC-GISCOSLDISCOVTGKLDISTELGKWINSSINALDK EE-NIK 20 AC-TYCKGSLDISCOVTGKLDISTELGKWINSSINALDK EE-NIK 20 AC-TYCKGSLDISCOVTGKLDISTELGKWINSSINALDK EE-NIK 20 AC-TYCKGSLDISCOVTGKLDISTELGKWINSSINALDK EE-NIK 20 AC-TYCKGSLDISCOVTGKLDISTELGKWINSSINALDK EI-NIK 20 AC-GISCOSLDISCOVTGKLDISTELGKWINSSINALDK EI-NIK 21 AC-GISCOSLDISCOVTGKLDISTELGKWINSSINALDK EI	271	Ac-LELDKWASLFNFF-NH2		
AC-ELGAVAINSISNALDIGLEENISCHOVAVICATETS-AHR2 AC-TELGAVANISISNALDIGLEENISCHOVAVICATETS-AHR2 AC-STELGAVANISISNALDIGLEENISCHOVAVICATETS-AHR2 AC-STELGAVANISISNALDIGLEESISKIGLOVAVICATETHR2 AC-STELGAVANISISNALDIGLEESISKIGLOVAVICATERIR2 AC-DISTELGAVANISISNALDIGLEESISKIGLOVAVICATERIR2 AC-DISTELGAVANISISNALDIGLEESISKIGLOVAVICATERIR2 AC-ALDISTELGAVANISISNALDIGLEESISKIGLOVAVICATERIR2 AC-ALDISTELGAVANISISNALDIGLEESISKIGLOVAVICATERIR2 AC-ALDISTELGAVANISISNALDIGLEESISKIGLOVAVICATERIR2 AC-ALDISTELGAVANISISNALDIGLEESISKIGLOVAVICATERIR2 AC-ALTIGALDISTELGAVIANISISNALDIGLEESISKIGLOVAVICATERIRA AC-ALTIGALDISTELGAVIANISISNALDIGLEESISKIGLOVATERIR2 AC-ALTIGALDISTELGAVIANISISNALDIGLEESISKIGLOVATERIR2 AC-ALTIGALDISTELGAVIANISISNALDIGLEESISKIGLOVATERIR2 AC-ACAVATIGALDISTELGAVIANISISNALDIGLEESISKIGLOVATERIR2 AC-ACAVATIGALDISTELGAVIANISISNALDIGLEESISKIGLOVATERIR2 AC-ACAVATIGALDISTELGAVIANISISNALDIGLEESISKIGLOVATERIR2 AC-ALDISCAVATIGALDISTELGAVIANISISNALDIGLEESISHIRIR2 AC-ALDISCAVATIGALDISTELGAVIANISISNALDIGLEESIHRIR2 AC-ALDISCAVATIGALDISTELGAVIANISISNALDIGLEESIHRIR2 AC-ALDISCAVATIGALDISTELGAVIANISISNALDIGLEESIHRIR2 AC-ALDISCAVATIGALDISTELGAVIANISISNALDIGLEENIHRIR2 AC-ACAGUSELDISCAVATIGALDISTELGAVIANISISNALDIGLEENIHRIR2 AC-ACAGUSELDISCAVATIGALDISTELGAVIANISISNALDIGLERIR2 AC-ACAGUSELDISCAVATIGALDISTELGAVIANISISNALDIGLERIR2 AC-ACAGUSELDISCAVATIGALDISTELGAVIANISISNALDIGLERIR AC-ACAGUSELDISCAVATIGALDISTELGAVIANISISNALDISTELGAVIANISISNALDISTELGAVIANISISNALDISTELGAVIANISISNALDISTELGAVIANISISNALD	272	Ac-LELDKWASLANWF-NH2		
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T No.	Sequence	 U	· :
** 365	AO-AIDHLRASLETTHOAIEAROAGGERILAVQGVOD-HH2		
366	AO-IDHLRASLETTHQAIEARQAGQEHILAVQGVQDY482		
367	AO-DHLRASLETTHQAIEAIRQAGQEHILAYQGYQDYHHIZ		
268	Ac-KLRASLETTHQAIEAIRQAGQEMILAYQGYQDYIN48H2		
269	Ao-LRASLETTHQAIEAIRQAGQEHILAVQGVQDYINHAHQ		
270	ACRASLETTHQAIEAIRQAGQEMILAYQGYQDYRRIE-RH2		
271	Ac-YTSVITIELSNIKENKUNGTDAVKLIKQELDKYK-1412		
372	Ac-TEVITIELENIKENKUNGTDAVKLIKGELDKYKN-KH2		
273	Ac-Sylthelshikehkuhgtdavklikoeldkykka-kih2		
274	Ac-Shirenkurgtdakykurgeldkyknaytelollahi2		
376	Ac-Kenkungtdakyklikgeldkyknavtelgillings-nh2		
. 276	Ac-CLELDKWASLWRWFC-NH2		
\$77	AO-CLELDKWASLANWFC-NH2		
278	Ac-CLELDKWASLFNFFC-NH2		
379	AC-YTSLIKSLIEESQNQQEIQHEQELLELDKWASLFNFF-NH2		
381	AO-RIAKOLEDKVEELLEKNYKLENELELDKWASLWKWF-KH2		
382	ACKVEELLEKKYHLENELELDKWASLWKWF-NH2		
383	Ac-RMKQLEDKVEELLSKLEWIRRSHQKLDSHAR2		
384	AC-RAKQLEDKVEELLSKLAFIRKSDELLHNV-NH2	•	
285	ACELEALRGELEALRGELELDKWASLWNWF-NH2		
386	Ao-LDPIDISIELNKAKSDLEESKEWIRRSHOKLDSI-NH2		•
387	Ao-CHEQLEDS:FTVEFFQV-HH2		
386	Ao-MAEDDPYLGRPEOMFH DPSLAND		
389	Ac-EDFSSIADRIDFSALLEGISS-NH2		
390	AO-TWOEWERKYDFLEENITALLEEAOIQQEKNILYELQ-NH2		
391	Ac-WOEWERKYDFLEENITALLEFACKQOEKNIAYELOKAKIZ		•
392	AS-QEWERKYDFLEENITALLEEAQKQQEKKKKYELQKQAKKZ		,
293	AGEWERKYDFLEENITALLEEACKQCEKRINYELOKUN 41142		,
294	AOWERKVOFLEENITALLEEACKQCEKNUYELOKLUS-NIIIZ		1
29 5	ACERKYDFLEENITALLEEACKGCEKKINYELCKLINSWAKKI		•
296	AO-RIKVOFLEENITALLEEAQIQQEKHILYELOKLISWD-HH2		•
297	AC-KVDFLEEHITALLEEAQIQQEKKINYELQIQLKSWDV-KIHZ		•
395	AC-VOPLEENTALLEEACIQCERRILYELOKLKSWDVF-10:12		
299	AC-OFLEENITALLEEAGEQGERHINYELQHILNSWIDVFG-1912		
400	AOFLEENTALLEEAGIQGERRINYELOKUNSWDVFGW4812		•
401	A O-LEENTALL EFACIOCEKNINYEL CICLASWDVFGHW-KIH2		
402	Ac-LEERITALLEEACHQQEIGHIYELQKLKSWDYFGKWF-KIHZ		
403	ACHEOSEERELYWAKEOLLDLLFHUFHOTVGAWIMQ-HH2		
405	A - QQQLLDVVKRQQELLRLTVWGTKHLQTRVTAIEKYLKD-KH2		
406 407	A COLLIDVIKE COELECTIVISTIC STRUTATE CYLLID CHILL		-
408	Acquidwirequelleltwigpkalqtevtalekylkdq4842		
409	Ao-DERKODKYLWOQTGTLOLTLIGLEKTAKLQWYRLKRY-4812		
410	AcqqqLDvvigqqqELRLTvwgTigH_QTRVTAEKY4H2		
411	A-COLDWIGQUELRLTWIGTIGHLQTRVTAMEKYLAH2		
412	A-GLLDWIGROGELIRLTWGTIGILGTRYTAIEKYLKHIH2		
413	A CLAWROOF LETTWICTKILCTRYTAIEKYLKO-KH2		
414	A-DWIGGOET FLYWGTIGH CTRYTATEGYLKDQ-HILZ		
415	A DVARQUELLELTY WOTT RECOTE VIA TAKEN LEDGLA 4812 A DVARQUELLELTY WOTT RECOTE VIA TEXT LEDGLA 4812		
416	VO NAMO DEL TATA MOLICATORIA LA PENTADO POLICA MARIA		

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No.	Gaquence	
417	ANTROGELLELTYWOTIQUI.QTTRYTAIERYLKDQAQLH4H12	
418	Ao-ROCELLRLTVWGTROLLQTRVTAIEKYLKDQAQLKA-1812	
419	AS-QQELLELTYWGTKYLQTRYTAIEKYLKDQAQLHAW-NH2	
420	Ac-QELLRLTVWGTKNLQTRVTAIEKYLKDQAQLHAWG-NH2	
421	AC-ELLRILTY-WGTKNILQTRYTAIEKYLKDQAQLHAWGC-NH2	
422	AO-HRILLRAIEAGGHILGLTVWGPKQLQARILAVERYLKDQ-NH2	
423	Ac-SELEKRYKNRVASRKCRAKFKOLLOHYREVAAAK-NH2	
424	AC-ELEIKRYKNRYASRKCRAKFKOLLOHYREVAAAKS-NH2	
425	AC-LEHRYIGHRYASRKCRAKFKOLLOHYREVAAAKSS-NH2	
426	AC-EIKRYMYRVASRKCRAKFKOLLOHYREVAAAKSSE-NH2	
427	AC-IKRYKHRYASRKCRAKFKQLLQHYREVAAAKSSEN-NH2	
428	Ac-KRYKNRVASRKCRAKFKQLLQHYREVAAAKSSEND-NH2	
429	Ao-RYKNRVASRKCRAKFKQLLQHYREVAAAKSSENDR-NH2	
430	Ac-yknrvasrkcrakfkqllqhyrevaaakssendrl-nh2	•
431	AC-KNRVASRKCRAKFKOLLOHYREVAAAKSSENDRLR-NH2	
432	AC-NRVASRKCRAKFKQLLQHYREVAAAKSSENDRLRL-NH2	
433	Ac-RVASRKCRAKFKQLLQHYREVAAAKSSENDRLRLL-NH2	
434	AC-VASRKORAKFKOLLOHYREVAAAKSSENDRLRLLL-NH2	
435	Ac-ASRKCRAKFKOLLOHYREVAAAKSSENDRLRLLLK-NH2	
436	AGSRKCRAKFKOLLQHYREVAAAKSSENDRLRLLLKQ-NH2	
437	Ac-RKCRAKFKOLLQHYREVAAAKSSENDRLRLLLKQM-NH2	
438	Ac-KCRAKFKOLLQHYREVAAAKSSENDRLRLLLKQMC-NH2	
439	AO-CRAKFKOLLOHYREVAAAKSSENDRLRILLKOMCP-NH2).*·
440	AG-RAKFKOLLOHYREVAAAKSSENDRLRILLKOMCPS-NH2	
441	Ac-AKFKQLLQHYREVAAAKSSENDRLRLLLKQMCPSL-NH2	
442	Ac-KFKQLLQHYREVAAAKSSENDRLRLLLKQMCPSLD-NH2	*
443	AO-FKOLLOHYREVAAAKSSENDRLRLLLKOMCPSLDV-NH2	.'
444	Ac-KOLLOHYREVAAAKSSENDRLRLLLKOHCPSLDVD-NH2	
445	Ac-CLLOHYREVAAAKSSENDRIJRILLIKOHCPSLDVDS-NH2	21
446	A-LLOHYREVAAAKSSENDRLRILLIKQIKCPSLDVDSI-NH2	•
447	Ac-LOHYREVAAAKSSENDRLRLLLKOHCPSLDVDSII-NH2	
448	Ac-QHYREVAAAKSSENDRLRLLLKOMCPSLDVDSIIP-NH2	
449	Ac-HYREVAAAKSSEHDRLRLLLKOMCPSLDVDSHPR-HHZ	
450	Ao-YREVAAAKSSENDRLRLLLKOMCPSLDVDSEPRT-NH2	
451 452	AO-REVAAAKSSENDRILRILLIKOMCPSLDVDSUPRTP-NH2	
462 453	Ac-EVAAAKSSENDRURLLLLKOMCPSLDVDSUPRTPD-NH2	
454	Ac-VAAAKSSENDRILRILLIKQIICPSLDVDSIIPRTPDV-NH2 Ac-AAAKSSENDRILRILLIKQIICPSLDVDSIIPRTPDVI-NH2	
455	Ao-AAKSSENDRIJRILLI KOMOPSI DVDSIIPRTPDVI H-NH2	
456	Ao-AKSSENDRURULIKONICPSUDVDSIPRTPDVLHE-NH2	
457	Aó-KBSENDRLRILLÍ-KOMCPSLDVDSIIPRTPDVLHED-NH2	
458	Ao-SSENDRLRLLLKOMCPSLDVDSIPRTPDVLREDLAVH2	
459	Ac-SENDRLRLLLKOMCPSLDVDSIIPRTPDVLHEDLL-KIH2	
460	Ac-ENDRURULLIKOMCPSUDVDSIIPRTPDVLHEDLLH-NH2	
461	Ac-KIDRLRILLIKOMCPSLDVDSIIPRTPDVLHEDLLKF-KH2	
634	Ac-PGYRWMCLRRFIFLFILLCLIFLLYLLDYQGMLAIH2	
635	Ao-GYRWIKCLRRFIIFLFELLOLIFLLVLLDYQGMLP-KH2	
636	Ac-YRMMCLRRFREI-FILLCLEFLLVLLDYQGMLFV-RH2	
637	AORWACI RETUTALLE TALLETTO GREEN ARE	
638	Acting and the little of Lythonical Pych 1/12	
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T No.	Sequence	
• 639	Acticles Fifther Lylldy Compyoplasiz	
- 640	A-CLRRFEFLFILLCLEFLLVLLDYQGELPVCPLLHIB	
- 541	Actrefieleillclielvldygghipvcplip-hiz	
- 642	Ac-RRFIEFLFILLCLIFLLVLLDYQGHLPVCPLIPG-NH2	
- 643	AS-RETIFICALIFICATION OF THE PARTY OF THE PA	
- 544	AO-FIRFILLICLIFLLVLLDYQGHILPVCPLIPGSS-HHZ	
- 645	ACCIFICATION OF THE PROPERTY O	
· 64 6	Ac-IFLFILLCLIFILVLLDYQGIRLPVCPLIPGSSTT-HH2	
- 547	Ac-FLFILLCLIFLLVLLDYQGKILPVCPLIPGSSTTS-KH2	
- 648	Ac-LFILLCLIFLLVILDYQGMILPVCPLIPGSSTTST-KH2	
- 649	Ac-FILLLCLIFLLVLLDYQGMLPVCPLIPGSSTTSTG-KH2	
• 6 60	Ac-ILLLCLIFLLVLLDYQGIKLPVCPLIPGSSTTSTGP-KH2	
· 6 51	Ac-LLLCLIFLLVLLDYQGIKLPVCPLIPGSSTTSTGPC-NH2	
· 652	Ac-LLCLIFLLYLLDYQGMLPVCPLIPGSSTTSTGPCR-NH2	
· 6 63	Ac-LCLIFLLVILDYQGMILPYCPLIPGSSTTSTGPCRT-NH2	•
664	Ac-CLIFLLYLLDYQGMLPVCPLIPGSSTTSTGPCRTC-NH2	
65 5	Ac-LIFLLYLLDYQGMILPYCPLIPGSSTTSTGPCRTCM-NH2	
6 56	Ac-IFLLVLLDYQGHILPVCPLIPGSSTTSTGPCRTCHT-HH2	
657	Ac-FLLVLLDYQGMLPVCPLIPGSSTTSTGPCRTCMTT-NH2	
658	AC-PLLVLQAGFFLLTRILTIPQSLDSWWTSLNFLGGT-NH2	
669	Ac-LLVLQAGFFLLTRILTIPQSLDSWWTSLKFLGGTT-KH2	
€60	Ac-Lylqagfflltriltipqsldswwt6lnflggttv-nH2	
561	AO-VLQAGFFLLTRILTIPQSLDSWWTELNFLGGTTVC-NH2	
5 62	AO-LOAGFFLLTRILTIPOSLDSWWTSLKFLGGTTVCL-KH2	
663	Ac-QAGHTLLTRILTIPQSLDSWWTSLKIFLGGTTVCLG-NH2	
664	Ao-AGHTLLTRILTIPOSLDSWWTSLKFLGGTTVCLGQ-KH2	,
665	Ac-GFFLLTRILTIPOSLDSWWTSLNFLGGTTVCLGQN-NH2	1
666	AO-FFILTRILTIPOSLDSYWTSLKFLGGTTVCLGCKS-KIHZ	v.*
667	Ac-FILTRILTIPOSLDSWWTSLNFLGGTTVCLGQNSQ-NH2	
6 68	AC-LLTRELTPOSLDSWWTSLNFLGGTTVCLGQNSQS-NH2	
670	AO-LITRILTIPOSLOSWATELNIFLGGTTVCLGQKSQSP-KH2	
671	AO-FWNWLSAWKDLELKSLLEEVKDELQKURANK2 HIKLRAKEAQQKILLOLTYWAKK2	
672	Ac-CGCHILLRAIEAQCHLOLTVWGIKOLQARILAVERYLKDQ-NH2	
673	YTSLIKSLIEESONQOEKKEGEL ELDKWASLWWF-KH2	
674	C13H27CO-YTSLIKSLIEESQNQQEIQHEQELLELDKWASLWWWF-NH2	
676	Ac-Avskgylsalrtgwytsyttelshikehkungtdanh	
676	A-GISHIETVIEFQQHQHRLLETREFSVHAGYTTPVS-HH2	
677	Ac-DOGROVICELLORLEPLYDGLRORDVIVSHOESH 4842	
676	Ac-YSELTHIFGDNIGSLOEKGIKLQGLASLYRTHITE-HH2	•
670	AC-TEITLQVRLPLLTRLLHTQIYRVDSISYHIQHREWY48H2	
680	Ac-YELAEYRRILLRIVLEPROALHALITCHIRPVQSYA-4642	
581	AO-SYFTVLSIAYPTLSEIKGVTVHRLEGYSYNKGSQEW4KH2	
682	Ao-Liceatricanosygssightivatics-hitz	
683	NHILLRAIEAQQHILLQLTVWGIKQLQARILAVERYLKDQ+NH2	
583	NNLLRAIEAQQHLQLTYWGKQLQARILAYERYLKDQ4H2	
684	OKOEPIOKELYPLTSL	
685	YPKF-WORTERIAT	
587	NGC CHOPS TO C.	
404	TO SECURITION OF THE PARTY OF T	

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No.	Sequence	· <u>-</u>
688	AORPOYYOH	
589	CLELDKWASLWNWFO-(cyclic)	
630	CLELDH(WASLAHWFC-(cyclic)	
591	CLELDKWASLANFFC-(cyclo)	
694	ACHINILIRAIEAQQQHILLQLTVWGIKQLQARILAVERYLKDQ-HH2	
695	Ac-CGGYTSLIHSLIEESQNQQEKNEQELLELDKWASLWNWF-NH2	
696	Ac-PLLVLQAGFFLLTRILTIPQSLDSWWTSLKFLGGT-KH2	
697	AC-LLYLQAGFFLLTRILTIPQSLDSWWT6LHFLGGTT-HH2	
698 .	AC-LYLQAGFFLLTRILTIPQSLDSWWT6LNFLGGTTV-KH2	
699	AC-VLQAGFFLLTRILTIPQSLDSWWTSLNFLGGTTVC-NH2	
600	AC-LOAGFFILTRILTIPOSLDSWWTSLNFLGGTTVCL-NH2	
601	Ac-QAGFFLLTRILTIPQSLDSWWTELNFLGGTTVCLG-NH2	
602	AC-AGFFLLTRILTIPQSLDSWWT5LNFLGGTTVCLGQ-NH2	
603	Ac-GFFLLTRILTIPQSLDSWWTSLNFLGGTTVCLGQN-NH2	•
604	A6-FFLLTRILTIPQSLDSWWTSLNFLGGTTVCLGQNS-NH2	
605	Ac-Filtraltiposldswwtslhflggttvclgonso-nih2	
€06	ACILITRILTIPOSLDSWWTSLNFLGGTTVCLGQNSQS-NH2	
607	Ac-LTRILTIPQSLDSWWTSLNFLGGTTVCLGQNSQSP-NH2	
608	Ac-Leldkwaslwwwa-nh2	ŧ
609	Ac-LELDKWASAWWYF-KH2	
610	AC-LELDKAASLWNWF-NH2	
611	Ao-LKLDKWASLWKWF-NH2	
612	AO-LELKKWASLYNWF-NH2	<i>:</i>
613	Ac-DELLHNYNAGKST-KIH2	. •
614	Ac-KSDELLHNVNAGKST-KH2	•
e 15 e 16	Ao-Africadellhinnagicst-nii2	;
6 17	AO-FDASISCIVIERUNOSIA FI-NIFIZ	
618	A6-YAADKESTOKAFDGITNKVNSVIEKMNTOFEAVGKE-NH2	•
619	Ac-Gytekuntofeavgkeegnlerrlenlnkrikedgelakk2	
620	Ac-WITYNAELLYLMENERTLDFHDSNYKNLYDKVRMOLAKH2	
621	AO-EWDREINNYTSLIHSLIEESONQOEKNEGEGGC-NH2	
622	Ac-INNYTSLIKSLIEESQNQQEKKEQELLELDKWASLARIZ	
623	AOHNYTSLIHSLIEESQNQQEKKEQELLE-KH2	
624	Ac-WINEWORENNYTSLIKSLIEESONQOEKNEQELLE-NH2	
625	AC-INTWINEWDREINNYTSLIKSLIEESQNQQERKEQELLELDKWASLWNWF-NH2	
626	A O IDISTELAKAKS DLEESKEWINGS NOOK LDSKINWH-HIHZ	
627	Ac-HOOEKNEOGELLELDKWASLWKWFRKTKWLWYTKKFF-KH2	
127	AO-HOOFICHEOFILLELDKWASCAMWIRKTHWILWYKOFI-KHZ	•
628 629	Ac-QNQQERREQELLELDKWASLWNWFRITTRWLWYRRF-RH2	
630	AO-GONGGERGEGELLELDKYASLWAWYRGTHWILWYRGHRIZ	•
. 631	Ao-ESCHQQEKKEQELLELDKWASLWKWFKITKWLWYIK-KKZ Ao-EBSCKQQEKKEDELLELDKWASLWKWFKITKWLWYI-KKZ	
632	A-FESCHQOEKREGELLELDKWASLWKWFRITKWLWY-4H2	•
633	AC-LIFES CHOOF KHEOFILE LOKWAS LWAWFRITH MLW-442	
634	Ac-SLIEESONOGERRIEGELLELDKWASLIMMWENTHWILARD	
63 5	Ac-HSLEESCHQOEKRECELLELDKWASLWARWFHITTWW-4142	
636	Ac-HISLE ESCHOOFINEDELLELDKWASLWKWHHTW48(2	
637	ACCRES ESCONOCIONICO EL EL DAVIAS MANTELLARIS	
638	ACCURATE SONO CERNEDELLE DRIVASI WRWITHIARIS	
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T No.	Sequence	·
(3)	ANTELNEL PERCHOCEGNECEL LEI DIGWASLARWINHARIZ	
640	ACHYTELEISLEESCHOOEGECELELDKWASLWAWARD	
641	ACHINYTELEHSLEESCHOOERHEOFLELDKWASLVIN-KIHZ	•
642	ACHINYTELHELIEEEQHQQEKKEQELLELDKWASLWAIHZ	
643	AC-EINHYTSLIHSLIEESQHQQERNEGELLELDKWASLARH2	
644	ACREMNYTELENSLIFESONOOFKNEGFILLFLDKWAS-NH2	
645	AC-DREINNYTELIHELIEESQHQQEKNEQELLELDKWA-NH2	
646	AC-WOREINNYTELINSLIFESONOGEKNEGELLEI DKWAH2	
647	AC-EWOREINNYTSLINSLIEESONQOEKNEOFI LEI DK-NIH2	
648	AC-MEWDRENNYTSLIKSLIFESQNQQEKNEQFILLFLD-NH2	
649	AC-WHEWPREINNYTSLIKSLIEESQNQQEKNEQELLEL-NH2	
650	AC-TWINEWDREINNYTSLIKSLIEESQNQQEKNEQELLE-NH2	
651	AC-MITWMEWDREINHYTSLIHSLIEESQHQQEKHEQELL-NH2	-
652	AC-HIMTWHEWDREINNYTSLIHSLIEESQNQQEKHEQEL-NH2	
663	AC-HINATWHEWDREINHYTSLIHSLIEESQHQQEKKEQE-NH2	
654	Ac-Winnerworeinnytslikslieesqhqqekneq-kh2	
655	AC-MANNITWMEWDREINNYTSLIKSLIEESQNQQEICNE-NIK2	
€56	AC-QIWMNIATWINEWDREINNYTSLIHSLIEESQNQQEIQN-NH2	
657	AC-EQIMNIMITWIMEWOREINNYTSLIHSLIEESQNQQEK-HH2	
658	Ac-LEQIWANINTWINEWDREINNYTSLIHSLIEESQNQQE-NH2	
659	AC-SLEOWHINITYMEWDREINNYTSLIHSLIEESQNQQ-HH2	
€60	Ac-KSLEOMANIATYMEWDREINNYTSLEHSLIEESQNQ-HH2	
661	Ac-HICSLEONWINNITWINEWOREINNYTSLIHSLIEESQH-HIH2	,
662	Ao-SLAFIRKSDELLHNYNAGKST-NH2	·
663	Ao-FDASISQVNEKINQSLAFIRK-NH2	•
664	AO-YTSLIHSLIEESQQQQEKQEQELLELDKWASLWKWF-KH2	
665	AO-FDASISQVNEKIHQSLAFIRKSDELLHNVNAGK-NH2	
666	Ao-FDASISQVNERDHOSLAFIRISDELLHHVNA-NH2	
667	Ac-FDASISQVNEKINGSLAFIRKSDELLHNV-NH2	
668	Ac-FDASISQVNEKINGSLAFIRKSDELLH-KH2	•
663	Ao-FDASISQVNEKINQSLAFIRKSDELAH2	
670	Ao-FDASISQVNEKINQSLAFIRKSD-NH2	
671 672	Ao-Asisqvitektikoslafirksoellirinvinagkst-kiriz	•
673	Ao-ISQVNERDINGSLAFRICEDELLHRIVINAGICST-RH2	
674	AO-QVNEKINGSLAFIRKSDELLHNYNAGKST-NH2 AO-NEKINGSLAFIRKSDELLHNYNAGKST-JH17	
675	A-KIKGSLAFIRICSDELLHWYNAGKST-KIHZ	
676	Ao-HOSLAFFREDELLHMMAGKET-KRIZ	
677	AO-FWWW.BAWKDLELYPGSLELDKWASLWKWF-KG12	
678	Ac-CGGHHLERAIEAOCHLOLTYWGHOLOARILAVERYLIDO-NH2	
679	ACCGOTTELHISLIEESCHOOEIGKEOELLIELDKWASLWHWI-NH2	
680	YTELESCHOOF RECELLE DIGWASLWAWF	
681	MINITANEAQCHILOLTYWGKOLQARILAYERYLKDQ	
682	A-EIGHYELDICKSWDVFTHWLDFTSWYRYIQYIQYGY40H2	•
683	Ac-QERRINYELORLNSWDYFTNWLDFTSWVRYYQYIQYG-RIH2	
684	Ac-QCERRINYELOKLHSWDVFTRWLDFTSWVRYIQYIQY-RH2	
68 5 .	Ac4QQEQUIYELOIQLISWDVFTKWLDFTSWVRYIQYIQ-(III)2	
686	Accidentification of the property of the prope	
687	As A COCCEDENTE CHE ASSESSED FOR THE DETERMINATION AND	
CEE	AcQAQCOEGRATELOKUSENDYFIKM DFIEW/RTQ 1812	

T. No.	Sequence		•
741	A-QQQHINLEAFAQQHILQLTVWQRQLQARIAVERYLHILE		
742	AC-VOQQNINLLRAIEAQQHILLQLTVWQNQLQARILAYERY4HIZ		
743	AO-IVQQQHILLERAIEAQQHILLQLTVWQHQLQARILAYER-HH2		
744	Ac-GIVQQQNNLLRAIEAQQHLLQLTVWQIXQLQARILAVE-NH2		
745	AO-EGTYQQQHINLLRAIEAQQHLLQLTYWGIKQLQARILAV-HIH2		
768	AGREMITATVOAROLLEGIVQQQNINLLRAIEAQQHLLQLTV-NH2		
760	Ac-GARSHITLTVQARQLLEGIVQQQHHLLRAIEAQQHLLQLAHI2		
764	AGGSTMGARSMILTVQARQLLEGIVQQQMILLRAIEAQQHHHH	2	
765	AC-GSTMGARSMILTVQARQLLEGIVQQQNNLLRAIEAQQH-NH:		
766	ACEGSTHIGARSHITLTVQARQLLSGIVQQQHHLLRAIEAQQ-HH2	2	
767	AC-RAKFKQLLQHYREVAAAKSSENDRLRLL-NH2		
768	Ac-AKFKQLLQHYREVAAAKSSENDRLRLLL-NH2		
769	Ac-KFKQLLQHYREVAAAKSSENDRLRLLLK-NH2		
770	Ac-FKQLLQHYREVAAAKSSENDRLRLLLKQ-NH2		
771	AC-RAKFKQELQHYREVAAAKSSENDRLRLLLKQMCPS-NH2		
772	DKWASLWNWF-NH2	•	
773	Biotin-FDASISQVNEKINQSLAFIRKSDELLHNYNAGKST-NH2		
774	Ac-ydasisqvnekingslafirksdellhivnagkst-kh2		
775	AC-YDASISQVNEKINQSLAYIRKSDELLHIVVNAGKST-NH2		
776	Ao-FDASISQYNEKINQSLAYIRKSDELLHNYNAGKST-HH2		
777	Ao-FDASISQYQEKIQQSLAFIRKEDELLHQYQAGKST-NH2		
778	Ac-FDASISQYNEKINQALAFIRKADELLHNYNAGKST-HH2		
779	Ac-FDASISQVNEKINQALAFIRKSDELLHKVNAGKST-KH2		•
780	Ac-FDASISQVNEKINQSLAFIRKADELLHNVNAGKST-NH2		
781	Ac-ydasisqyqeeqqalafirkadelleqyqagkst-hihi2	•	
782	Ac-FDASISQVNEIGNOSLAFIRKSDELLENVNAGKST-KIHZ		•
783	AO-FDASISCYNEEINOSLAFIRKEDELLHIVVNAGKST-NH2		•
784	Ac-Vitedefdasisqvnekingslafirksdellenv-nitz		
785	Ac-VITISDEFDASISQVNEEKQSLAFIRKSDELLENV-NH2		• *
786	AC-YYPSDEYDASISQVHEEINQALAYIRKADELLENV-NH2		•
767	Ac-VFPSDEFDASISQVNEEINQSLAFIRKSDELLHNV-NH2		
768 789	AO-SNKSLEOWNWITWINEWDREIWNYTSLIHSLIEESQ-NH2		
790	Ac-WSNRGLEONWRIGHTWHEWDREINNYTSLHSLIEES-NH2		
791	AC-SWINGSLEONWRIGHTWINEWDREINHYTSLIKSLEE-KH2		
792	AC-ASWSKICSLEOWKKIKTWIKEWDREIKKYTSLIKSLIE-KIKZ AC-KASWSKICSLEOWKKIKTWIKEWDREIKKYTSLIKSLI-KIKZ		
793	AOWNASWSKICELEONWININTWILEWOREINNYTSLINSLANI(2		
793	AOWNASWSHICSLEDWHINITWINEWOREINHYTSLRISLANI2		
794	AOPWNASWENINSLEONWINITWILEMORERINYTSLINS-NINZ		
705	AC-VPWNASWSNKSLEOWNINGTWINEWDREINNYTSLEH-NH2		
796	ACAVPWNASWSKICELEOKYNINITWIKEWDRENNYTELLHILZ	•	
797	AC-TAYPYNYASWSHIKSLEONYNYMITWINEWDRENNYTSL-NH2		
798	ACTTAYPWHASWSHKSLEQHWHRMITWHEWDREIKHYTS-KH2		
800	AC-AAASDEFDASISQVNEIGNQSLAFIRKSDELLHNV-NH2		
8 01	AC-VFPAAAFDASISQVNEKINQSLAFIRKSDELLHNV-NH2		
8 02	AC-VFPSDEAAASISQVNEKINQSLAFIRKSDELLIHV-KH2		
803	AC-VFPSDEFDAAAAQVNEKINQSLAFIRKSDELLHKV-HH2		
804	AC-VFPGDEFDASISAAAEKINGSLAFIRKEDELLIHV-1812		
805	ACTIFEDEFOASISCYNAAHOSIAFEKSDELLINV4612		
906	Activate Olispy Property Control of the Control of		A Section 1

T No.	Sequence	• -	
- 807	Ao-A/FPSDEFDASISQV/REKUNOSAAAIRKSDELLHRV-NGIZ	-	
808	AC-VITEDETDASSOVNIERINOSI AFAAASDELLINVARID		
809	AO-VIPSDETDASISQVNEKINOSLAFIRKAAALLIRIV-NIN2		
810	Ac-VFPSDEFDASISQVNEKINOSLAFIRKSDEAAANV-NIHZ		
011	Ac-VFPSDEFDASISQVREKINGSLAFRKSDELLAAA-NH2		
812	Ac-MYPSDEFDASISOVNEKINOSLAFIRKSDELLKINV-KH2		
813	AC-AAAAHSLIFESONOOEKREOFI LELDKWASLWNWF-NH2		
614	Ac-YTSLIHSLIFESQQQQEKNEQELLELDKWASLWKWF-KH2		
815	AC-YTSLIHSLIEESONOOEKOEOELLELDKWASLWNWF-NH2		
816	A-CIWHNIATWMEWDREINNYTSLIHSLIEESCHOOEKO-NH2		
817	Ac-QIWANNETWMEWDREINNYTSLIFISLIEESQQQQEKN-NH2		
818	AC-QWANNITWIMEWOREINNYTSLIHSLIEESQQQQEKQ-NH2		
819	AONKSLEQIMNINITYWEWDREINNYTSLIKSLIEESQQ-NK2		
820	AC-FDASISQVNEKINQSLAFIEESDELLHNVNAGKST-NH2		
821	Ac-ACIRKSDELCL-NH2		
823	AC-YTELEHSLEESONOOEKDEOFILELDKWASLWAWF-WH2		
824	Ac-YTSLIKSLIEESQDQQEKNEQELLELDKWASLWNWF-NH2		
825	Ac-YTSLIHSLIEESQDQQEKDEQELLELDKWASLWAWF-NH2		
82 6	AC-YTSLIHSLIEESQHQQEKNEQELLELDKWASLWDWF-NH2		
841	Ac-LEANITOSLEOAOIQOEKNILYELOKLNSWDYFTNWL-NH2		
842	AC-LEANISASLEQAQIQQERRILYELQKLNSWDYFTHWL-NH2		
643	AG-LEANISALLEQAQIQQEKNINYELQKLNSWDVFTNWL-NIH2		
844	AC-LEANITALLEQAQIQQEKKINYELQKLNSWDVFTNWL-NH2		
845	AG-LEANITAS LEQACIQUE KILIYELQKLINSWDVFTNWL-NH2		
845	Ac-LEANITASLEOACIQCEKNIYELCKLNSWDVFTNWL-NH2		
846	AO-RAKIFKOLLOHYREVAAAKSSENDRLRLLLKOMUPS-NH2		
847	Ac-Abu-DDE-Abu-MINSVKHGTYDYPKYEEESKLNRNEIKGVKL-NH2		
866	Ao-WQEWEQKVRYLEAKISQSLEQAQIQQEKKINYELQKIKIH2		
860	A-DEYDASISQVNEKIKQSLAFIRKSDELLKKVNAGK-KIHZ		
861	AO-YTELHSLIEESCHOOEKHEGELLELDKWASLWH-KH2		
862 ·	AO-YTSLIHSLIEESQHQQEKNEQELLELDKWASLW-NH2		
863	AO-YTELIHELEESQHQQEKKEQELLELDKWASLAKK2		
864	ACYTELIKELIEESCHOOFIKIEGELLELDKWAS-KIIIZ		
8 66	Ac-QARQLLEGIVQQQHILLIRAIEAQQHLLQLTVWGIKQLQARILAVERYLKDQ-KH2 Ac-DREINNTTELIKSLIEESQNQQEIQIEQELLELDKWASI WNWF-NH2		
867	Ac-KKIMTVMEWDREIKNYTSLIKSLIEESQNQQEKREQELLELDK-KKI2		
868	ACYTELHISLIEESCHOOEILEI DRWASI WAAA-NH2		
069	AOYTELIKSLIEESONOOEKKEOELLELDKIKAAAAKWEAKI		
870	ACYTELHELEESCHOOFKHEOFILEI DAAASLWAWF-NIF2		
871	ACYTELHISLIEESCHOOFKRECELLAAAKWASLWAWFARH2		
872	ACYTELEISLIEESCHOOEKREOAAAELDKWASLWINWFARIZ		
873	ACYTELHELEESCHOOEKAAAFILELDKWASLWKWF-WHZ		
674	ASYTELHISLEESCHOAAAHEGELLELDKWASLWKWF-HH2		
876	ACYTSLIKSLEESAAAQEKKEQELLELDKWASLWNWF-KK12		
876	ACYTELHISLIAAAONQOEIRIEDELLELDKWASLWKWF-KH2		
877	ACYTELHAAAEESONOOEIGIEGELLELDKWASLWKWF-11112		
876	ACYTEAAASLIEESCHQQEICHEGELLELDKWASLWKWF-NH2		
679	AO-ENNIKATYMENDREKERDIOSLAFRIKSDELLIRIY-NILZ		
880	Ac-VISE/NEEHOSLAFRKADELLENVDKKASLINKTF-1812		
्र दश्य	AGENTINATION OF THE PROPERTY O		

T No.	Sequence	• :	
822	YTELHELEESONOOEKHEDELLELDKWASLWWFMG4842		
883.	- AONEKHOSLAFIRKSDELLIRIVARIE	•	
884	BIOGO-YOPLVFPSDEFDASISQVNEKINQSLAFIRKSDELAH2		
885	·BIOHIT-PLYFPSDEFDASISCYNEKINGSLAFIRKSDELLH-KH2		
286	BIOGRA-VFPSDEFDASISQVNEKINQSLAFIRKSDELLHNV-NH2		
887	BIOTIN-DEFDASISOVNEKINOSLAFIRKSDELLHNYNAGK-NH2		
255	Biotin-VYPSDEFDASISQVNEKINQSLAFIRKSDELLHNV-NH2		
889	Biotin-YYPSDEYDASISQVNEEINQALAYIRKADELLENV-NH2		
2 90	Ac-VYPSDEFDASISQVQEEIQQALAFIRKADELLEQV-KH2		
891	AC-HYTELHISLIEESONQQEKHEQELLELDKWASLWNWF-NH2		
6 92	AC-HNYTELHISLIEESONOGENHEGELL ELDKWASLWNWF-HH2		
693	AO-INNYTSLIHSLIEESQNQQEXHEQELLELDKWASLWNWF-KH2		
294	AGEINNYTSLINSLIEESQNQQEKNEQELLELDKWASLWNWF-NH2		
895	AC-YTSLIHSLIEESQNQQEKNEQELLELDKWASLWNWFN-NH2		
E96	AC-YTSLIHSLIEESQHQQEKHEQELLELDKWASLWWWFRI-NH2		•
897	AC-YTSLIFSLIFESCHQQEKHEQELLELDKWASLWNWFRIT-KH2		
898	AC-YTSLIHSLIEESQHQQEKHEQELLELDKWASLWHWFHITH-HH2		
6 99	AO-YDPLYFPSDEFDASISQVNEKINQSLAFIRKSDELLHNVNAGK-NH2		
900	AC-NYTSLIHSLIEESONOOEKNEOELLELDKWASLWAWFN-NH2		
901	AC-HINYTSLIFSLIFESQNQQEKHEQELLELDKWASLWWWFNLWH2		
905	Ao-KCRAKFKOLLOHYREVAAAKSSEKDRLRLLLKOMCPSLDVDSIIPRTPD-NH2		
906	AO-RAKIFKQLLQHYREVAAAKSSENDRLRLLLKQMCPSLDVDSIIPRTPD-NH2		
907	Ac-VYPSDEYDASISQVKEEKQALAYIAAADELLEKV-KH2		
207	Ac-YDASISQVNEEINQALAYIRKADELL-NH2		. /
910	Ac-44-44-44-44-44-44-44-44-44-44-44-44-44		
911	Ao-KNGTYDYPKYEEESKLNRNEIKGVKLSSKGVYCH4H2		· .
912	AO-VTEKQMASDNINDLIQSGVNTRLLTIQSHVQNYLNH2		
913	CHOCERHEDELLEIDKWASLWAWF-KH2	.*	
814	Ao-CHOCERTECEL ELDKWASLWWWF-NH2		.5
916	LWNWF-RH2		•
216	ELLELDKWASLWWWF-KH2		
917	EKNEGELLELDKWASLWNWF-NH2		
818	SLIEESONOOEKKEOELLELDKWASLWAWF-NH2		
919	AC-YTSLIKSLIFESONOOEKKEOFILELDKWASLWWW		
920	AC-YTSLINSLIEESONOOEKNEOELLELDKWASLWN		
821	AO-YTSLIHSLIEESONQQEKKEQELLELDKWASLW		
822	AC-YTSLIHSLIEESQHQQERNEQELLELDKWASL		
923	TELHISLIEESQHQQEIQHEQELLELDKWASLWWWF-KH2		
824	SLIKSLIFESONOQEINEQELLELDKWASLWKWF-KIK2		
825	LINSLIEESONQOEIQIEOELLELDKWASLWWWF-NH2		
926	M-SLEEDSON-QOEKRECIELLELDKWASUWWW-KKIZ		
840	AO-AAYALLPAVILALLAPSELEKRYKKRYASRKORAKFKOLLOHYREVAAAKAKK2	·	
941	AO-AAYALLPAVILALLAPCRAKFKOLLOHYREVAAAKSSEKDRIRILLIKOMCP-KHIZ		
842	AC-YTSLIHSLIEESQHQQEKNINIERDWEMWTMNINWIQ-NH2		
944	VYPSDEYDASISQVNEEINQALAYIRKADELLENV4IH2		
945	Ac-LINGLARGLINGLARGUSCLARGUSRLESA-NH2		
946	Ac-WMEWDREIKHYTELIKSLIEESQHQQEKKEQELLAKK2		
947	ANDREWRYTELHELEESCHOOLIGERHEOFILELAND		
948	AS ENDRE NATIONAL RISE DESCRIÇOS PRESENTANTOS DE LA LIBERTA		
949	Action result is the second of the second in		2

T Ha	Sequence	
960	BIOGO WHIS EMORERANTELHISLEESCHOOEKRECELLELATIE	
951	AC-YLEYDRENINYTSLINSLIEBSCHOOEIGKEGELLELANIZ	
852	Ac-KOFHINYOEVGKANYA-HH2	
623	Ao-IRKSDELL-KIH2	
854	Decanoyl-tricsDELL-titl2	•
955	Acetyl-Ace-Ace-IRKSDELL-NH2	
856	Ac-ydasisqv-11H2	
957	AO-KEKINQSL-KIH2	
858	Ac-SISQYNEEINQALAYIRKADELL-NH2	
859	AC-QVNEEINQALAYIRKADELL-NH2	
960	AC-EEINQALAYIRKADELL-NH	
961	ACHQALAYIRKADELLAH2	
962	Ac-LAYIRKADELL-NH2	
863	FDASISQVNEKINQALAFIRKSDELL-NIH2	
864	AC-W-NIG-EWDREINNYTSLIHSLIEESQNQQEKNEQELLEL-NH2	
965	Ac-Asrkcrakfkollohyrevaaakssendrlrlllkomcpsldvds-nih2	
967	AC-WILEWOREINNYTSLIHSLIEESQNQQEKNEQFILLEL-NH2	
968	Ac-yvkgepiinfydplyfpsdefdasisgynekingsl-nh2	
\$69	AC-VYPSDEYDASISQYNEEINQSLAYIRKADELLHINV-NH2	
870	Ac-ydasisqyneeinqalayirkadellenv-nH2	
971	Ac-ydasisqyneeinqalayirkadelle-nih2	
872	Ac-VYPSDEYDASISQYNEEINQALAYIRKAAELLHIVV-NH2	
873	AC-VYPSDEYDASISQVNEEINQALAYIRKALELLHINV-NH2	
874	Documoyi-YTSLIHSLIEESQNQQEKNEQELLELDKWASLWNWF-NH2	
6 75	AC-YYPSDEYDASISQYNEEINQLLAYIRKQ.DELLENV-NH2	
976	Ac-DEYDASISQYNEKINQSLAFIRKSDELLAH2	
877	Ao-GNDQGSGYAADKESTQKAFDGTTNKVNSVIEKTHT-NH2	
. 978	AO-ESTOKAFDGITHKVHSVIEKTHTOFEAVGKEFGKILEKR-NH2	
679	AO-DGITHKVNSVIEKTHTQFEAVGKEFGHLEKRLENLHK-KH2	<i>;</i>
960	AO-OSNVIQILYDKVRSQLRDHVKELGHGAFEFYHK-NH2	,
188	AO-ROMYKELGHGAFEFYHKADDEALMSVKNGTYDYPKY-HH2	
982 983	Ac-EFYHKADDEALNSVKHGTYDYPKY-NH2	
964	AO-AAVALLPAVILALLAPAADKESTOKAFDGITNIKVNS-NIH2	•
885	AO-AAVALLPAVILALLAPAADSHVKRILYDKVRSQLRDH-NH2	
986	Ao-Kestqkafdgithkvrsv-rih2 Ao-Kektntqfeavgkefgnler-rih2	
987	Ao-RILENIANCE DE LOWITH MELLY ALENE AND 2	
988	A-SHVKKLYDKVRSQLRDH-HBHZ	
889	Ac-WINEWORERRYTELERS LIES ON QUERREDELANTE	
890	AOMMEWDRERRYTELHSLIEESCHQCERRECE-KH2	
891	Ac-MEMOREMNYTSLINSLIEESCHQQEIQNEQELANIZ	
992	AC-MEMORENNYTSLIKSLIEESCNOOERNEGE-NIKE	
893	A DEWORENNYTELINGUEESCHOOEIGNEGELLE-NINZ	
894	AGENDRENNYTSLIKSLIEESONOOEIONEOELLANK	
695	AO-EMDRENNYTSLINSLIFESCHQQEIQNEQEL-NIH2	
696	AC-YTKFTYTLLEESCHOOEKKECELLELDKWAGLWNWF-NH2	
897	AO-YMKOLADSLHOLAROVERLEBA-HHZ	
808	ACYLMOLARGIROLADSLIKOLARGYSRLESA-KH2	*
699	A O YOU WERKY DELEGATALLE ENGAGE CHECKEL CHILARITE	
1000	A-MINANCA MINITER SEES OF THE	

T		•
No.	Sequence	
- 1001	A6-YASILAALIEESQHQQEIQIEQEILELAKWAALWAWF-KKI2	
1002	(Ao-ENDREIMYTSLINSLIEESONQOERREQEGGC-HRZ/dimer	
1003	Ao-ydisielnikakedleeekewikkenqkldskonwh-kki	
1004	Blotiny-I-DISTELNKAKSDLEESKEWIKKSNQKLDSIGNWH-NH2	
1005	Ac-YTELI-OH	
1006	Fmoo-HSLIEE-OH	
1007	Fmoc-SQNQQEK-OH	
1008	FMOO-NEQELLEL-OH	
1009	Fmoo-DKWASL-OH	
1010	Fmoo-WNWF-OH	
1011	AC-AKTLERTWOTLNHLLFISSALYKLNLKSVAQITLSI-NH2	
1012	AC-HITLQAKIKQFINMWQEVGKAMYA-NH2	
1013	Ac-LENERTLDFHDSNVKNLYDKVRLQLRDN-NH2	
1014	Ac-LENERTLDFHDSHVKNLYDKVRLQLRDHVKELGNG-NH2	
1015	Ac-tldfhdshvkhlydkvrlqlrdhvkelgngafef-nh2	

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1016	AO-DISIELRIKAKSDI EESKENIKKSHOKI DSKRIVII-KEIZ	
1021	BioGoyl-SISQVNIEEHQALAYIRKADELLAH2	
1022	Biotiny1-61SQVNEETHQSLAYTRKGDELLAH2	
1023	Ao-SISQVNEEINQSLAYIRKSDELLAIN2	
1024	A O-IDISIEL NIKAKEDLEESKEWIEKEN QELDSIGNWE-NIHZ	
1025	AC-IDISIELNIKAKSDI. EESKEWIKKSNOEL DSKGNWH-NIH2	
1026	AO-IDISIELNIKAKEDI EEAKEWIKKANQKI DSIGNWH-HIH2	
1027	AC-IDISIELNIKAKSDLEESKEWIKKAHQKLDSKRWH-NH2	
1028	AC-IDISTELNIKAKSDILEEAKEWIKKSNOKLDSKINWH-NH2	
1029	BIOUNY-HISVALDPIDISIELNIKAKSDLEESKEWIKKSNOKL-NH2	
1030	Biotinyl-ALDPIDISIELNKAKSDLEESKEWIKKSHQKLDSI-NIH2	
1031	desAminoTyrosine-NSVALDPIDISIELHKAKSDLEESKEWIKKSNQKL-NH2	
1032	desAminoTyrosine-ALDPIDISIELNKAKSDLEESKEWIKKSNQKLDSI-NH2	
1033	Ac-ydasisqyneeinqalafirkadelaih2	•
1034	AC-YDASISQVNEEINQSLAYIRKADELLAH2	
1035	Blodnyl-YDASISQVNEEIKQALAYIRKADELL-KIH2	
1036	Blofinyl-YDASISQVNEEINQSLAFIRKSDELLAH2	
1037	AO-YDASISQVNEEINQSLAFIRKSDELLAHZ	
1038	AC-MLEWDREINNYTSLIHSLIEESQNQQEKNEQEL-NH2	
1039	BIOTINY-IDISIELNKAKSDLEESKEWIRRSNOKLDSIGNWH-NH2	
1044	AC-YESTOKAFDGITHKVKSVIEKTHTQFEAVGKEFGNLEKR-KH2	
1045	Biotin-DEYDASISQVNEKINQSLAFIRKSDELLAH2	
1046 .	AC-MEWOREINNYTSLIKSLIEESONQOEKKEOELL KIKZ	
1047	AC-WQEWEQKVRYLEANISQSLEOAQIQQEKNIKYELAH2	7
1048	AC-WOEWECKVRYLEANISOSLEOAQIQQEKNEYEL-NH2	
1049	Ac-WQEWEQKVRYLEANITALLEQAQIQQEKNEYEL-NH2	•
1060	AC-WOEWECKVRYLEAKITALLEOAQIQQIEGUMYEL-KH2	
1061	AC-WOEWECKVRYLEAKISQSLEQAQIQQEKKEYELQKLAVI12	
1052	AC-WOEWECKYRYLEANITALLECACKQCERCIEVELCKLANI:2	
1063	AC-WOEWECKYRYLEANITALLECACKQEKNINYELOKLAKK2	
1054	Ac-IDISIELNKAKSDLEESKEWIEKSHOKLDSIGNWH-NH2	
1055	AGEFGRILENCHRIKRVEDGFLDYWTYHAELLYALENE-KIHZ	
1056	ACEDGELDWITYNAELLYLMENERTLDFHDSHYKRILYDKVRIKOLAKK2	•.
1057 1058	Ao-EISCHVIEIGNGSLAFIRKSDELLANIE	
1059	desaminoTyr-SISQVNEKINQSLAFIRKSDELL-NH2	
1060	Accisovneringslayirksdellaritz	
1061	Ac-QQLLDWYGRQQEMLRLTVWGTKHLQARYTAIEKYLKDQ-NH2 YTSLIHSLIHESQHQQEKHEQELLELDKWASLWKWFC	
1062	AO-FDASISQVIEIGROSLAYIROSDELL-NIR	
1063	ACYTELERSCHOOLIKREOFILE DKWA	
1064	Indois-3-acctyl-DEFDASISQVNEKINQSLAFIRKSDELLAH2	
1065	Indois-3-cocyl-DEFDESISQYKEKIKQSLAFIRKSDELL-KIHZ	
1066	Indole-3-acetyl-DEFDESISQVHEKIEQSLAFRKSDELLARI12	
1067	Indole-3-ecotyl-DEFDESISQVHERIEESLAFIRKSDELL-HI-12	
1068	Indole-3-ecotyl-DEFDESISQVNEKIEESLOFRKSDELL-KIHZ	
1069	Indole-3-ecetyl-GGGGGDEFDASISQVNEKGKQSLAFRKSDELL-KH2	
1070	2-Hispitroyi-DEEDASISQV/NEIQHQSLAFIRKSDELLANIZ	
4071	doublety-Defdaciscy-New Newscalar Williams	
1072	MOGGAL DPIDSTEL NIKANSDICEESKE WRRENON LIST HELZ	
1073	Ac-PDASSOVNERONOALXYTER (DELLERYNAGEST-4812)	
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T. No.	Segrence	
1074	ACAYPEDEYDASISQYNEKINQALAYEKADELLINVARIA	
1075	ACAYPEDEYDASISQYNEKIKQSLAYIRKSDELLHIV-HH2	
1076	AO-HIGHGYGYG-Hit2	
1077	Ac-YGWGWGF-NH2	
1078	ACHYQEYEQKYRYLEANITALQEQAQIQAEKAEYELQKLANH2	
1079	ACHYOEWEOKYRYLEAEITALQEEAQIQAEKAEYELQKIL-NIH2	
1081	AC-YTELIKELIFESONQOEKNEOFLLELDKWAS	
1082	ACAMPEDEFDASISOVNEKINOSLAFIRKSDELLKKV-NH2	
1083	Ac-SKHISEOIDOIKKDEOKEGTGWGLGGKWWTSDWGY-NH2	
1084	Ac-LEKNISEOIDOIKKDEOKEGTGWGLGGKWWTSDWG-NH2	
1085	Ac-DLEKKISEGIDQIKKDEQKEGTGWGLGGKWWTSDW-KH2	
1086	Ac-EDLSKNISEQIDQIKKDEQKEGTGWGLGGKWWTSD-NH2	
1087	AC-IEDLEKNISEOIDQIKKDEQKEGTGWGLGGKWWTS-NH2	
1088	Ac-GIEDLEKNISEQIDQIKKDEQKEGTGWGLGGKWWT-NH2	
1089	AC-IGIEDLEKNISEQIDQIKKDEQKEGTGWGLGGKWW-NH2	
1090	2-Napthoy1-PSDEFDASISQVNEKINQSLAFIRKSDELLHINVN-NH2	
1091	AC-AYPSDEYDASISQVNEKINQALAYIRKADELLENV-NH2	
1092	ACAYPSDEFDASISOVNEKINOALAFIRKADELLENVAH2	
1093	AC-AYPSDEYDASISQVNEKINQALAYIREADELLENV-NH2	
1094	BIOHIMYLYDASISCYNEKINGSLAFIRESDELL-NH2	
1095	AC-AIGIEDLEKNISEOIDOKKDEOKEGTGWGLGGKW-NH2	
1096	AC-AAIGIEDLEKNISEQIDQIKKDEQKEGTGWGLGGK-NH2	,
1097	Ac-DAAIGIEDLSKNISEOIDQIKKDEQKEGTGWGLGG-NH2	
1098	Ac-PDAAIGIEDLSKNISEQIDQIKKDEQKEGTGWGLG-NH2	•
1099	AC-NITDKIDQUKDFYDKTLFDQGDNDNYWYTGWRQWI-NH2	
1100	A-KKITDKIDQIIHDFVDKTLPDQGDKDKWWTGWRQW-KIH2	•
1101	Ac-TKHITDKIDQIIHDFVDKTLPDQGDNDHWWTGWRQ-NH2	
1102	Ac-WTIGHTDIGDQIIHDFVDKTLPDQGDNDNWWTGWR-NH2	
1103	Ac-DWTKRITDKDQIIHDFVDKTLPDQGDNDNWWTGW-NH2	
1104	Ac-HDWTKKITDKDQSIHDFVDKTLPDQGDNDNWWTG-NH2	
1105	Ac-PHDWTKNITDKIDQIIHDFVDKTLPDQGDNDNWWT-NH2	
1106	Ac-EPHDWTKHITDKIDQIIHDFVDKTLPDQGDHDHWW-NH2	
1107	A-AEPHIDWITKHITDKIDQIIHDFVDKILPDQGDHIDHW-HH2	
1108	Ac-ALEPHOWTICHITOKODOSHOFVOKTLPDQGDNDN-NIH2	
1109	Ac-AAIEPHIDWTIGHTDKIDGIIHDFVDKTLPDQGDHD-HH2	
1110	Ac-DAAIEPHDWTKNITDKIDQIIHDFVDKTLPDQGDN+IH2	•
1111	Ac-Leptvyleviyminyywgpslysilepflpllpiff-nih2	
1112	Ao-Gleptvynleviwiniwywgpslysilspflpllpif-kii12	•
1113	AC-MGLEPTVMLEVIMINIMYMGPSLYSILEPFLPLLPHHIZ	
1114	AOFYGLEPTYWLEYIWMMWYWGPSLYSILEPFLPLLP-KH2	
1116	AC-WFVGLEPTVWLEVIWIRWYWGPELYEILEPFLPLLAUI2	
1116	Ac-OMFVGLSPTVYVLSVIWMMWYYVGPSLYSILSPFLPLANH2	•
1117	Ac-VCWFVGLEPTVWLEVWMMMWYWGPSLYSILEPFLP-NH2	
1118	AO-FYCWFYGLEPTVWLEVTWINIWYWGPELYEILEPFLACH2	
1119	AO-PFVQWFVGLEPTVWLEVIWIMMYWGPSLYSILEPF-NH2	
1120	Ao-VPFVQWFVGLEPTVWLEVTWMMWYWGPSLYEILEP-KH2	
1121	AOLYPFYCHFYCLEPTYWLEYTHILLWYWCPELYEILE-HHZ	
1122	H-KHTTWKEHDRENKYTSLIKSLIEDSCNOOEKHECELLELDKW-OH H-CAROLLBGWOOGKHLRAEAGGNLOLTWKGROLGARKAYERYLKDO-OH	
1123 1124	Actifications of the property	
1141	NOT IT SOUTH THE	

T No.	Securence	· .
1125	Ac-Vitedetoasisqviterikoslaykreadellenv-kriz	
1126	Accepasis CVN EGY CSLAY READELL KKIZ	
1127	Ao-Nedelleldkwasi.nnwpggggdefdasisgvnekingslafirksdellahi.	
1128	Aoleldkwaslwww.fgggdefdasisgvwekingslafirksdellani2	-
1129	2-Naphihoy1-EGEGEGEGDEFDASISQVNEKINQSLAFIRKSDELLAH2	
1130	Ac-Asrkcrakfkollohyreyaaakssendrlrlllkoncpsldv-nh2	
1131	2-Haphthoyl-GDEEDASISQVHEKINQSLAFIRKSDELL-NH2	
1132	2-Naphthoyl-GDEEDASESQVNEKINQSLAFIRKSDELL-HH2	
1133	2-Naphthoyi-GDEEDASESQQNEKINQSLAFIRKSDELL-NH2	
1134	2-Naphthoyl-GDEEDASESQQNEKQNQSLAFIRKSDELL-NH2	
1135	2-Naphthoy1-GDEEDASESQQNEKQNQSEAFIRKSDELL-NH2	
1136	Ac-WGDEFDESISQVNEKIEESLAFIRKSDELL-NH2	•
1137	Ac-ytslggdefdesisgynekieeslafirksdellggwwwf.nh2	
1138	Ac-ytslihslggdefdesisqvnekteeslafirksdellggwaslwnwf-nh2	•
1139	2-Naphthoyl-GDEFDESISQYNEKIEESLAFIRKSDELL-NH2	
1140	2-Haphthoyl-GDEEDESISQVKEKEESLAFIRKSDELL-KH2	
1141	2-Naphthoyl-GDEEDESISQVQEKIEESLAFIRKSDELL-NH2	
1142	2-Naphthoyt-GDEEDESISQVQERGEESLLFIRKSDEIL-NH2	
1143	Biotin-GDEYDESISQVNEKIEESLAFIRKSDELL-NH2	
1144	2-Naphthoyl-GDEYDESISQVNEKIEESLAFIRKSDELLANH2	•
1145	AC-YTSLIHSLIDEQEKIEELAFIRKSDELLELDKWNWF-NH2	
1146	VYPSDEYDASISQVNEEINQALAYIRKADELLENV-NH2	
1147	ACHRILLRAIEAGGHILLGLTVWGSKGLOARILAVERYLKDQ-NH2	
1148	GGGVYPSDEYDASISQVNEEINQALAYIRKADELLENV-NH2	7
1149	AC-HALLRAIEAGGHILGLTVWGEKOLOARILAVERYLKDQ-HH2	
1160	Ac-PTRVNYILEGVLVLAbuEVTGVRADVHLL-HH2	•
1161	Ac-PTRVHYLEGYLVLAbuEVTGVRADVHILLEQPGNLW-NH2	
1152	AGPEKTPLLPTRVNYILIGVLVLABUEVTGVRADVHILLARIZ	.*
1163	AHAGGGYYPSDEYDASISCYNEEINQALAYIRKADELLENY41H2	<i>.</i> *
1155	Ac-YTSLERSLGGDEFDESISQVNEKDESLAFIRKSDELLARIZ	
1166	ACYTELGGDEFDESISCYNEIGEESLAFIRKEDELLANIE	
1167	Ac-DEFDESISQVNEKIEESLAFIRKSDELLGGWASLWKWF-41H2	
4168	A DEFDESISONNERGESLAFIRKSDELLGGWWWF41H2	
1169	AC-YTSLIKSLIFESCHOOFICKEOFILELDKASLWHWF-HH2	
1160	AC-YTSLIKSLEESCHQOEKREGELELDKSLWKWF-KH2	
1161	Ac-YTSLIKSLIEESCHQOEKREGELLELDKLWKWF-KK2	
1162	Ac-YTSLIKSLISESONQOEKKEGELLELDKWKWF-NK2	
1163	AC-AITWINEWOREINNYTSLIKSLIEESQHQQEIQKEQELLELDKASLWWWF-KH2	
1164	AC-ATTWINEHOREMHYTSLIKSLIEESONQOEICKEOELLELDKSLWWWF-KIKZ	
1165	AC-AITWINEHOREIKNYTSLEHSLEESONQOEKHEOELLELDXILWKWF-KIHZ	
1166	AC-AITWINEWORERRYTSLERSLEESONQOEGREGELLELDKWWWF-KH2	
1167	AC-AITWINEH/DREINNYTSLIKSLIEESONOOEKKEOELLELDKWASLKIN-KII(2	
1168	AC-ANTWINEWOREDWYTSLINSLEESCHOOEKNEOELLELDKWASLANIZ	
1169	(Pyr)KWSY(2-mapthyl-D-AlayLRPG-KH2	•
1170	AO-WMWFDEFDESISQVNEKIEESLAFIRKSDELLWMWF-KH2	
1171	Ac-YTSLEHSLEESONOOEKNEOELLELDKYASLYNYF-NHZ	
1172	ACYTELHISLEESCHOOFICHEOFILIELDKYAYLYRYF-KIIZ	
4673	2 Hisphthoyl-AcsAcsAcsDEFDESISQYHERIEESLAFIRKSDELLACsAcsAcsAcsAcsWADD	
1174	2-Haphthoyl-AcaAcaAcaGDEFDESISOVHERDEESLAFRKSDELLGAcaAcaAcaMunity	
1176	2-Haptmayi-GOET-DESISOVICE DESIGNATION OF THE STATE OF TH	

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1176	2-Haphthoyl-GDEFDESISQVNEKEEERLAFFEESDELLAVH2	•
1177	AC-WOEWEOKVNYLEANITALLEGACIOCOERNEYELCKLANI2	
1178	AC-WOEWECKVDYLEANITALLECACIOCIERNEYELCKLANIA	
1179	AC-WOEWEOKVRWLEANITALL EDAGKOOFKNEYFLOKLANIS	
1180	AC-WOEWEKOVRYLEANITALLEOAGIOGEKNEYELOKL-NH2	
1181	AC-WOEWEHOVRYLEANITALLEOAGIQGEKNEYELOKI_NH2	
1182	AC-WOEWEHKVRYLEANITALLEOAGIQGEKNEYELOKU-NH2	
1183	Ac-WQEWDREVRYLEAKITALLEGAGIQQEKNEYELOKI_AKH2	
1184	Ac-WQEWEREVRYLEANITALLEQAQIQQEKHEYELOKLAVH2	
1185	Ac-WQEWERQVRYLEANITALLEQAQIQQEKNEYELQKL-NH2	
1186	AC-WQEWEQKVKYLEANITALLEQAQIQQEKNEYELOKLAHI2	
1187	AC-WQEWEQKVRFLEANITALL EQAQIQQEKNEYELOKLAVH2	
1188	Ac-VNaIPSDEYDASISQVNEEINQALAYIRKADELLENV-NH2	
1189	Ac-VNaIPSDENaIDASISQVNEEINQALAYIRKADELLENV-NH2	
1190	Ac-VNaIPSDEYDASISQYNEEINQALANAIIRKADELLENV-NH2	
1191	AC-VYPSDEFDASISQVNEIQHQSLAFIREADELLFRIFF-RIH2	
1192	Ac-VYPSDEYDASISQVNEEINQALAYIRKADELLFNFF-NH2	•
1193	AC-YTSUTALLEGAGIGGERNEYELOKLDKWASLWMWF-NH2	
1194	AC-YTSLITALLEQAQIQQEKNEYELQKLDKWASLWEWF-NH2	
1195	Ac-YTSLITALLEGAGIQGEKNEYELGKLDEWASLWEWF-NH2	
1196	AC-YTSLITALLEOAQIQQEKNEYELQELDEWASLWEWF-NH2	
1197	AC-YTSLITALL FEAQIQQEKNEYELQELDEWASLWEWF-NH2	
1198	Naphthoyf-Aus-Aus-Aus-TALLEQAQIQQEKNEYELQKLAus-Aus-Aus-W-HH2	
1199	AC-WAAWEQKVRYLEANITALLEQAQIQQEKNEYELQKLANI12	<i>:</i>
1200	AC-WOEAAQKYRYLEAHITALLEQAQIQQEKHEYELQKLAHI2	
1201 .	AC-WQEWAAKVRYLEANITALLEQAQIQQEKNEYELOKLAHZ	•
1202	AC-WQAAEQKYRYLEANITALLEQAQIQQEKNEYELQKLANIZ	•
1203	AC-WOEWEAAVRYLEANITALLEQACKQOEKNEYELOKLANK2	
1204	AC-WOEWEQAARYLEANITALLEQAQIQQEKKEYELQKLAKI12	
1205	AO-MOEWECKAAYLEANITALLECACIQCEKKEYELOKLAUI2	•
1206	AO-WOEWEOKVAALEANITALLEOAGIQGEKNEYELOKIL-KH2	
1207	AC-WOEWEOKYRYLEANITALLEDAO!QOEKNEYELOKLGGGGWASLWNF-NH2	•
1206	2-Naphthoyl-GDEFDASISQVNEKHQSLAFTRKSDELT-KI12	•
1209	2-Haphthoyl-GDEFDASISQVNEKINQSLAFTRKSDELT-NH2	
12 10	2-Naphiboyl-GDEFDASISQVNEKTHQSLAFTRKSDELT-KH2	
1211	2-Haphthoyl-GDEFDASISQTNEKTHQSLAFTRKSDELT-NH2	
1212	2-Naphthoy1-GDEFDASTSQTKEKTHQSLAFTRKSDELT-NH2	
1213	2-Naphiboy4-GDEYDASTSQTHEKTHQSLAFTRKSDELT-KH2	•
1214	2-Naphthoyl-GDEFDEESQVKEIGEESLAFRKSDELLAUI2	
1215	2-Haptathoyl-GDEFDASISQVNEKINQSLAFIRKSDELA-KIH2	
12 16 12 17	2-Haphthoyl-GDEFDASASQANEKANQSLAFARKSDELA-NH2	
1217	2-Haptathoyl-GDEFDESISQVNEKIEESLAFTRKSDELL-KIH2	
1219	2-Naphthoyl-GDEFDESISQVKEKTEESLAFRKSDELLAKH2	
1220	2-Naphthoyl-GDEFDESISQTREKREESLAFIRKSDELLARI2	
1221	2-Haptithoyl-GDEFDESTSGVNERGESLAFIRKSDELL-NH2	•
1221	AO-WAWFDEFDESTSQVNERIEESLAFRKSDELLWNWF-NH2 AO-WAWFDEFDESTSQTNERIEESLAFRKSDELLWNWF-HH2	
1223	AO-MANDEFDESTSCHIERTEESLAFRASDELLMMWF-1812	
4234	Aoloacetlingingosipsidistratigatyangg	•
1225	ACTINITILE ESCALATE DE TELEVANISTE DE LA COMPANIONE DE LA	
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1226	AC-WOENEGKVRYLEANTALLEDAGIOGERREYELOKUDKWASLWRWRAII2	
1227	ACHRILITATION MEDICARITALLEDA OF OCENTEY ELOK LONGVAS LYNNWF-1712	
1230	AO-WMWFTEESDELLWWWF-titl2	
1231	2-Haphthoyl-GFIEESDELLW-HH2	
1232	AO-WFIEESDELLW-RIF2	
1233	2-Naphtinoyl-GFNFFIEESDELLFNFF-NH2	
1234	2-Kaphthoyl-GESDELW-Kit2	
1235	AC-WINWFGDEFDESISQYQEETEESLAFTEESDELLGGWNWF-NH2	
1236	AC-WAWFHSLIEESQNQQEKNEGELLELDKWASLWHWF-NH2	
1237	AC-YTSLITALLEGAQIQQEENEYELQELDEWASLWEWF-KH2	٠.
1238	Ac-ytslihslggdefdesisovneeieeslafieesdellggwaslwwwf-nh2	
1239	2-Naphthoyl-GDEFDESISQVQEEIEESLAFIFESDELL-AH2	
1240	H-QAROLLSSIMQQQHHLLRAIEAQQHLLQLTVWGIKQLQARILAVERYLKDQ-QH	
1241	Ac-CPKYVKQNTLICLATGMRNVPEKQTR-NH2	
1242	Ac-GLFGALAGFIENGWEGHIDGWYGFRHQNSC-NH2	
1243	Ac-LNFLGGT-NH2	
1244	Ac-LDSWWTSLNFLGGT-NH2	
1245	Ac-ELTIPQSLDSWWT5LHFLGGT-NH2	
1246	Ac-GFFLLTRILTIPOSLDSWWTSLNFLGGT-NH2	
1247	AC-WQEWEQKITALLEQAQIQQEKNEYELQKLDKWASLWNWF-NH2	
1248	ACHMWFITALLEQAQIQQEKNEYELQKLDKWASLWNWF-KH2	•
6249	ANY MENERICALLEDA GIOCERNEYELON DINWAS LINEWEN HIZ	•
1250	AO-WOEWEOKVRYLEANITALLEGAQIQQEIGEYELQIKLARIZ	
1251 1252	AC-WOEWEOKVRYLEAGITALLEGAGIQGEKIEYELQKLAUHZ	
1253	Ao-KENKANGTDAKVKLKOELDKYKNAVTELQLLKOS-NH2	
1264	Ac-HIKENKANGTDAKVKLIKQELDKYKNAVTELQLLM-NH2	,
1255	(FS)-YTSLHSLEESONQOEKREOELLELDKWASLWWWF-NH2	<i>,</i>
1256	2-Kaphthoyl-GWNWFACADEFDESISQVQEEEEESLAFIEESDELLACAWNWF-NH2 Ac-WMWFGDEFDESISQVNEIGEESLAFIEESDELLGWNWF-NH2	₹
1257	Ao-WWWFGDEFDESISQV/NEKIEESLAFIRKSDELLGW/NWF-WH2	
1258	AO-WAWF-Aca-DEFDESISQVAERGEESLAFRKSDELL-Aca-WAWF-AH2	
1259	Ac-WMWF-Aca-DEFDESISQVKERGEESLAFIEESDELL-Aca-WMWF-Wit2	
1260	A-EESCHOOFICHELFLOKWANIC	
1261	EESCHQQEKKEGELLELDKWA	
1262	Ac-CGTTDRSGAPTYSWGANDTDVFVLNHTRPPLGHWFG-NH2	
1263	Ao-GVEHRLEAACHWITRGERADLEDRORSELSP-KH2	
1264	Ao-Cyreghasrawyaytptyatrogklpt-46H2	
1266	Ao-Creprehiwiticidahasiypg-hihz	
1266	Ao-LOHYREVAAAKSSEKDRIJRILLIKOHOPSLDVDS-KH2	
1267	AO-WQENDRESHYTSLITALLEQAQIQQEIQNEYELQKLDEWASLWEWF-NHZ	
1268	AO-CWOENDREISHYTSLITALLEOAOIQQEIRIEYELQIKLDEWASLWEWFC-NH2	
1269 127 0	A SWOENDRESSHYTSLITALLEGACIQUERREYELCKLDEWENFARK	
1271	Ao-CWOENDREISNYTSLITALLEQACKQOEKKEYELOKLDEWEWFC-HH2	
1272	Ao-GQHSQSPTENHSPTEAPPTAPGYRWA-NH2	
1273	Ac-PGSSTTSTGPARTALTTAQGTSLYPSA-4812	
1275	Ac-PGSSTTSTGPARTALITAQGTSLYPSAAATKPSDGHATA-HH2 Ac-WQEWDREITALLEQAQGQEGGEYELQKLDKWASLWKWF-KH2	
1276	A-WOENDRETALLEDACIOCIERIEVELORI.DEWASLWEWF4812	
1277 ::	Ac-WOENDRETALLEGACIOCERRETE DICTORNETE REP	
1278	WOULD SHELD IT THE TO TO COLUMN TO THE TO THE TOTAL TO TH	15 44 6 1
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No.	Security
1270	ANY DEMERSTALLEGACIO DER REVELO KLIEWENT-NILL
1280	AC-WOISVERETALLEGACIQUERIEVELOR DEWENT-W12
1281	AC-WOEWEITALLEQAQIQQEKHEYELQKLDEWEWF-NH2
1282	AC-WQEVIETALLEQAQIQQEKHEYELQKLIENEWF-KIHZ
1283	Ac-WOEWETALLEOACIQOEICEYELORIDEWEWF-NH2
1284	AC-WOEWETALLEDACIOCETEYELOICLEWEWF-NH2
1285	AC-WQEWDREIDEYDASISQVNERINQALAYIREADELWEWF-NH2
1286	Ac-WOEWEREIDEYDASISQVNERINQALAYIREADELWEWF-NH2
1257	Ac-WQEWEIDEYDASISQVHEIDINQALAYIREADELWEWF-NH2
1258	Ac-WQEWDREIDEYDASISQYKEEINQALAYIREADELWEWF-NH2
1289	Ac-WQEWEREIDEYDASISQVNEEINQALAYIREADELWEWF-NH2
1290	AC-WQEWEIDEYDASISQVNEEINQALAYIREADELWEWF-NH2
1291	AC-WQEWDEYDASISQYNEKINQALAYIREADELWEWF-NH2
1292	Ac-WQEWDEYDASISQVNEEINQALAYIREADELWEWF-NH2
1293	AC-WOEWEOKITALL EOAGIQOEKEYELOKLIEWEWF-NH2
1294	Ac-WQEWECKTALLEOACKQCEKEYELOKLEWASLWEWF-NH2
1295	ACWQEWEITALLEOAQIQQEKIEYELQKLIEWASLWEWF-NH2
1298	-vypsdeydasisqvneeinqalayirkadellenv-nih2 Ac-vvvypsdeydasisqvneeinqalayirkadellenvwnwf-nih2
1299	YTSLIHSLIEESCHQOEKNEGELLELDKWASLWMWF-NH2
1300	AC-WOEWDEYDASISQVNEKINQALAYIREADELWAWF-NH2
1301	AC-WQAWDEYDASISQVNEKINQALAYIREADELWAWF-NH2
1302	AC-WOAWDEYDASISQVIEKINQALAYIREADELWEWF-NH2
1303 1304	Blottn-YDPLYFPSDEFDASISQYNEKINQSLAFIRKSDEL-NH2
. 1305	Biofin-YDPLVFPSDEFDASISQVNEKINQSLAF-KH2
1206	BIOTIN-QVNEKINQSLAFIRKSDELLHNVNAGKST-KH2
1307	Ac-WRIEWDRE-HH2
1306	Ac-WOEWECK1-18-12
1309	AC-WOENEDKITALLEDAQKQOEKTEYELQKLIKWASLWEWF-NIKZ
1310	AC-WOEWEOKITALLEGACIQGEKIEVELOKLIEWASLWEWF-NH2
1311	AC-WOEWEREISAYTSLITALLEOAGKOCEKTEYELOKLEWEWF-KH2
1312	AC-WOEWEREISAYTSLITALLEOAOROCEKTEYELOKEWEWF-NHZ
1313	AC-WOEWEREISAYTSLITALLEDADIQUEKTEYELOKEWEW-NH2
1314	AC-WOEWEREISAYTSLITALLEDAQIQQEKTEYELQKLIEWEW-NH2
1315	Ac-FRESDHSESIQROFOLLRIGGRANIGGVDSDPIGSWLR-KH2
1316	Ac-DHSESIQIAGFQLLIKAGHVNKAGYDSDPIGSWLRGIF-NH2
1317	AC-WSVKQANLTTELLGDLLDOVTERHAVLQHRA-HH2
1318	Biotin-Willewores-NH2
1319 1320	BIOGIN-HIGHTWHIEWDREINNYTSLAUIZ AO-GAASLTLTVOAROLLSGIVQQQNRLLRAUFAQQHILLAUIZ
1321	AO-ASITITYOAROLLSGIYQQQHRILLRAEAQQHILLQLARIZ
1222	AC-VEYGHTLYYVNKQEGKGLYVKGEPHNFYDPLVF-NH2
1323	Acchwaygurpg-NH2
1224	AO-WOEWEOKIOHWSYGLRPGWASLWEWF-NH2
1325	Ac-WOEWEORIGHWSYGLRPGWEWF-NH2
1326	Ac-uniwechwsyglepgwnwf-4H2
1327	Aoffiffehwsyglepgfffffilia
1328	Acquantinisyaliffanano-1812
1329	PLINOAGHT THE TROS DESCRIPTION TO
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4221	Ac-WOEMEONTALLEOAO(OCERTEYELON) AEWASI WENTANII 2
C222	ACHICEMEONTALL EDACIOCIERAEYELORI AERIKASI WENFARIH2
1333 .	Ac-WOEWEONTALLEOAGIOGEKAEYELGKLAEWASLWAWF-NH2
1234	AC-WOEWECKITALLEOAGIOCEKAEYELCKLAKWASLWAWF-RFI2
1235	AC-THKAVVELENGVEVLTEKYLDLKNYDKOLLPIVNIK-NIZ
1336	Ac-KAVVELENGVEVLTEKVLDLKNYIDKOLLPIVNKOS-NH2
1237	Ac-WOEWEGKITALLEOAGIOGERRIEYELGKLIEWEWF-NH2
1238	Ac-WOEWECKITALLEOAOKOCEKGEYELOKLIEWEWE-NEW2
1239	Ac-WOEWEOKITALLEOAGIQOEKIEYELOKU.DKWEWF-NH2
1340	Ac-YDPL-VFPSDEFDASISQVNEKINGSLAF-NH2
1341	Fluor-VYPSDEYDASISQVNEEHQALAYIRKADELLENV-NH2
1342	Fluor-YTSLIRSLIFESONOOFICKEOFIL FLDKWASLWWW-NH2
1344	A&SGIVQQQNNLLRAIEAQQHLLQLTVWGIKQLQARILAH2
1345	Ac-QQQNNLLRAIEAQQHILLQLTVWGIKQLQARILAVERYLKDQ-NH2
1346	A S G TY O O O O O O O O O O O O O O O O O O
1347	Ac-WOEWEGKITALLEOAGKGEKKEYELGKLAEWASLWAWF-RIH2
1248	AO-WQEWEQKITALLEQAQIQQEKNEYELQKLAEWASLWAW4KH2
1349	Ac-WOEWEGKITALLEOAGKOEKAEYELGKLAEWASLWAW-4KH2
1350	Ac-WOEWEOKITALLEOAQIQQEKNEYELQKI.AEWAGLWAWF-KH2
1351	Ac-WQEWEQKITALLEQAQIQQEKKEYELQKLAEWAGLWAW-KH2
1162	AO-WOEWEOKITALLEOAQIQQEKAEYELQKLAEWAGLWAWAKK2
1253	AC-WOEWEONTALLEOAQIQGEKNEYELOKLDKWAGLWEWF-NH2
1254	Ac-WDEWOHWSYGLRPGWEWF-NH2
1366	AC-WOAWOHWSYGLRPGWAWF-NH2
1256	BIOTHY HAVE WEGKITALLE GAGAGGER KIEYELOKLOK WAS LWEWF- NH2
1357	WOEWECKITALLEGACIOGERIEYELOKLOKWASLWEWF
C368	WOEWECKITALLECACIOCIEXIEYELCKLIEWEWE
1361	Ac-AGSTRIGARSHITLTVQARQLLEGIVQQQNNLLRAIEAQQ-NH2
1362	Ac-AGSAMGAASLTLEAGSRTLLAGIVQQQQQLLDVVKRQQAN12
1363	AGAGSANGAASTALTAQSRTILLAGVQQQQQLLDVVKRQQAVH2
1364	A-ALTAGSRITLLAGIVQQQQQLLDVVKRQQELLRLTVWGT-KH2
1365	AC-TLEAGSRITLLAGIVQQQQQLLDVVKRQQEMLRLTVWGT-NH2
4366	Ac-TLTVOARQLLEGIVQQQHILLIRAIEAQQHLLQLTVWGHHIIZ
1367	Ac-WQAWIEYEAELSQVKEKIEQSLAYIREADELWAWF-HH2
1368	Ac-Woawieyeaslsoakekieeskayireadelwawf-kii2
C369	Ac-WQAWIEYERILLYQAKI.KIAKILYIAKELLEWAWR-KH2
4370	AC-WOAWIEYERLLVQVKLKIAIALLYIAKELLEWAWF-KIHZ
1371	AO-WOAWIELERLLYQYICLKIALKELLEWAWR-NH2
1372	Ao-GEWTYDDATKTFTVTEGGH-KH2
1373	Ac-WOEWEOKIGEWTYDDATKTFTVTEGGHWASLWEWF-NH2
1374	Ao-GEWIYDDATKTFTVTE-KH2
1376	AC-WOEWEOWIGEWTYDDATKTFTVTEWASLWEWF-NH2
1376	Ao-Airrettyrr-Air
1377	AO-WOEWEOKUMERFDYRTWASLWEWF-NH2
1378 1379	Ac-MINISTEGG-HILL
1320	Ac-Woeneokoukrenwstoggwaslwewf-nii2 Ac-Mirefnwst-nii2
4361	Ac-MOEMEORGHRERMETWASI MEMEARIA
1322	AOLLYPLARIETHSSYHOGO HRIZ COMPANY
4963	A-WOEMECKELLYPLAREITHESSYHOOGWAELWEWFILET
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T No.	*	•	•
	Seguence		·
1384	Activities viii in a martine and a martine a		
1365	AC-WOENEQKILLVPLARINTNISSVHWASLWEWF-HH2	•	
1366	TALLEGACIQQEKNEYELQKLDK	•	
1387	AO-TALLEQAQIQQEKNEYELQKLDK-NH2	• •	
1388	AO-TALLEQAQIQQEKIEYELQKLIE-NH2		
1389	TATTEOYO!GOEKIEAETOKITE -		
1390	Ac-QARQLLSGIYQQQNXLLRAIEAQQHLLQLTVWGIKQLQARILAVERY-NH2		
1391	Rhod-QARQLLSGIVQQQNNLLRAIEAQQHLLQLTVWGIKQLQARILAVERY-NH2		
1392	Ac-GAASLTLEAQSRTILLAGIVQQQQQLLDVVKRQQEML-NH2		
1393	Ac-GSAMGAASLTLEAQSRTLLAGIVQQQQQLLDVVKRQQEML-HH2		
1394	AO-PALETGLIHLHQNIVDYQFLFGYGSSIASWAIKWEY-NH2		
1395	Ao-PALETGLIHLHQNIVDVQFLYGVGSSIASWAIK-NH2		
1396	Ac-LETTQWQVLPUSFTTLPALETGLIHLHQNIVDVQY-NH2		
1397	AC-FRKFPEATFSRUGSGPRITPRUMYDFPFRLWHY-NH2		
1398	Ac-DFPFRLWHFPUTINYTIFKVRLFVGGVEHRLEAAUNWTR-NH2		
1299	Ac-yvggyehrleaaunwirgerudledrorselsplann2		
1400	MYYPSDEYDASISQVNEEINQALAYIRKADELLENV		
1402	Ac-GPLLYLOAGFFLLTRILTIPQSLDSWWTSLHFLGG-HH2		
1403	Ac-LGPLLVLQAGFFILTRILTIPQSLDSWWTSLNFLG-NH2		
1404	AC-FLGPLLVLOAGFFILTRILTIPOSLDSWWTSLNFL-NH2		
1405	AO-YTHTTYTLLEESQHQQEKNEQELLELDKWASLWHWF-NH2	•	
4406	YTHTYTLLEESQNQQEKNEQELLELDKWASLWNWF		
1407	AC-YTGIYNILLEESONQOEKNEGELLELDKWANLWNWF-NH2		
1408	YTGIYKLLEESQNQQEKNEQELLELDKWANLWKWF		
1409	AC-YTSLIYSLLEKSQKQQEKKEQELLELDKWASLWKWF-KH2		.:
1410	YTELYELLEKSQIQQEKNEQELLELDKWASLWNWF		i i
1411	Ao-EKSQIQQEIQIEQELLELDKWA-KIK2		
1412	EKRONOGEKNEGETT ETDKKKY		
1413	A-EDADIGOEKKEYELGIGUKKKAKIHZ	•	* * **
1414	EONOGOERNEYELDIA DIONA		
1416	AC-YTALHSLDESONOOXKEGELXELDKWASLWKWF-NH2		
1416	AC-YTXLHSLDXESQHQQXXHEQELXELD-NH2		
1417	AOYTSLIKSLIEESCHQCEKKECELLELD-KK2		
1418	AO-WOENEKITALLXOAOKOXKKEYELXKLDKWASLWEWF-KH2		
1419	A-XXTALLXQAQIQQXXXEYELXXLDXXXASLWEWF-NH2		
1420	Ac-WQEWEXKITALLXQAQQQXXXVEYELXXQLD-KH2		
1421	. AC-WECKITALLECACIOCIERREYELOKID-NHZ		
1422	AO-WEDGTALLXQAQIQQXIQVEYELXIGLD-NH2		
.1423	A-XXITALLXQAQIQQDIQKEYELXIQLD-KH2		
1425	A-QKITALLEQAQIQQEKNEYELQKI.D-KH2		
1426	A-OKITALLEOAQIQQEKKEYELQKLDKWASLWEWF-KH2		
1427	AO-WOEWEOKITALLEOAOKOOEKKEYELOKID-KH2		
1428	AO-YYPEDEYDASISQVHEENQALAYIRKADELLEN-OH		
1429	AO-YYPSDEYDASISQVNEEINQALAYIRKADELLE-OH		
1430	AC-MYPSDEYDASISQVINEETHQALAYTRKADELL-OH		
1431	AC-YYPSDEYDASISQYNEEHQALAYIRKADEL-OH		
1432	YPSDEYDASISQWIEERQALAYIRKADELLENVARI2		
1433	PSDEYDASISCY/REENCALKYRKUDELLERY-4812		
4434	GDETPAGESOVIESTION TRIVOSTISTIVANO		
1436	CERTIFICATION OF THE PARTY OF		

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_ Ho	Gentience	
1436	AC-TYPEDEYDASISQYDEERIQALAYRKADELLENY-1812	
1437	AC-VYPEDEYDASISQVINEEDQALAYRKADELLENV-NINZ	
1438	Ac-VYPSDEYDASISQVNIEENQALAYRKADELLEDV-4IH2	
1439	Ac-VYPSDEYDASISQYDEEDQALAYRKADELLENV-KH2	
1440	Actenikavyslengyevltekyldliknyidkollp-kihz	
\$441	VOTELHKVAARTENGAEAFTEKATDITÄÄÄIDKÖTTEHHIY	
1442	Ac-STHKAVVSLENGVSVLTEKVLDLKHYIDKQLLPIV-NIH2	
1443	Ac-Thkavvelehgveyltekyldlkhytdkollpivn-kih2	
1444	AO-NKAVVSLEHGVSVLTEKVLDLKRYDKOLLPIVNK-NH2	
1445	Ac-Kavvelengvevltekvldlknydkollpivnko-nh2	
1446	AC-AVVSLENGVSVLTEKVLDLKNYIDKQLLPIVNKQS-NH2	
1447	Ac-VVSLENGVSVLTSKVLDLKNYIDKQLLFIVNKQSU-KH2	
1448	Ac-vslengvsvltekvldlknyidkqllpivnkqsus-kh2	
1449	Ac-Slengvevltekvldlknyidkollpivnkosusi-nih2	•
1450	Ac-Lengvevltekvldlknyidkollpivnkosusis-nih2	
1451	A6-SHGVSVLTSKVLDLKHYIDKOLLPKYKKQSUSISH+KH2	
1462	Ac-NGVSYLTEKYLDLIKNYIDKOLLPYYNKOSUSISNI-NH2	
1453	Ac-GVSVLTSKVLDLIKHYIDKQLLPIVNKQSUSISNIE-NH2	
1454	A6-VSVLTSKVLDLKNYIDKQLLPIVNKQSUSISHIET-NH2	
1455	Ac-Syltskyldlknyidkollpiynkosusisniety-nih2	
1456	Ac-VLTSKVLDLKHYIDKQLLPIVNKQSUSISHIETVI-HHZ	
1457	Ac-LTSKVLDLKHYIDKQLLPIVNKQSUSISHIETVIE-NH2	
1458	AC-TSKYLDLKHYIDKOLLPHYNKQSUSISHIETVIEF-NH2	,
1459	Ac-SKYLDLKHYTDKQLLPIYNKQSUSISHTETVTEFQ-HH2	•
1460	Ac-KYLDLKHYIDKQLLPIVNKQSUSISHIETVIEFQQ-NH2	•
1461	Ac-VLDLKKYIDKQLLPIVKKQSUSISKIETVIEFQQK-KIH2	
1462	Ac-LDLKHYIDKQLLPIVNKQSUSISHIETVIEFQQKH-NH2	
1463	Ac-DLKKYTOKQLLPTYNKQSUSISKIETYIEFQQKRIN4KH2	
1484	Ao-LKNYIDKQLLPIVNKQSUSISNIETVIEFQQKNINRAH2	·
1465	Ac-KRYTOKOLLPKYNKQSUSISNIETVIEFQQKKNRLANII2	·
1466	AO-HYIDKOLLPIVNIKOSUSISNIETVIEFQQKNINRLLAIH2	
1467	Ac-YIDKOLLPIVIKQSUSISKIETVIEFQQKQKIRLLE-KIII2	
1468	Ao-IDKOLLPIVNIKQSUSISNIETVIEFQQKNNKRLLEHNIZ	
1459	Ao-DKOLLPIVHKOSUSISKIETVIEFQQKKKRLLEIT-KHZ	
1470	A-KOLLPIVNKQSUSISKIETVIEFQQKKKRLLETR-KHZ	
1471 1472	A-CALPIVNKQSUSSNETVIEFQQKNNRLLETTRE-NH2	
1673	AO-VYPSDEYDASISQVXIEEINQALA QVXIEEINQALAYTRKADIELLENV-KIHZ	
1474	VYPSDEYDASISQVNEERQALAYRKADELLENV	
1475	AO-DEYDASISQVNEENQALAYREADEL-KIK2	
1476	A-DEYDASISQYNERROALAYIREADELAH2	
1477	A-DOECLESVERGTYDFPROTEEESRILERREKGVELS-REIZ	
1478	Ac-DDE-Abu-LHSVKHGTYDFPKFEEESKLHRHEIKGVKLS-HH2	
1479	ACYTICODECLISSICIONITION REPORTED SKILLING REPOR	
1480	Acytik-Abu-DDE-Abu-Likeviqkotfdfpkreeesiklkirkeikovkres-kihz	
1481	ACYTELHISLEESCHQCEKNECELLELDHWASLWAWF-HH2	•
1482	ACTELHISLEESCHOOEKHEYELLELDKWASLHANNFLIST	
1463	AGYTELEBELEESCHOOFICHEYELLELDHINGSSMANNIGER	
1484	ACTICLES CONTROL OF THE PROPERTY OF THE PROPER	
1485	Consulation of the Consulation o	
	The state of the s	

T. No.	Seguence
1496	ACYTELHELIEESCHQQEIQEYELCKLDKWASLWHWF-4H12
1417	AC-YTSLIFFSCHOOPINGELCKLDKWASLWNWF-NH2
1488	AC-YTSLIHSLISESQHQQEIQIEQIELLELDKWASLWEWF-NH2
1489	ACYTELIHELIEEEQIQQEKNEQELLELDKWASLWEWF-NH2
1490	ACYTELHSLIEESQHQQEKHEYELLELDKWASLWEWF-NH2
1491	AC-YTSLIHSLIEESQIQQEKNEYELLELDKWASLWEWF-NH2
1492	ACYTSLIKSLIEESQKQEKKEYELQKLDKWASLWEWF-NH2
1493	AC-YTSLIHSLIEESQNQQEINEOELQKLDKWASLWEWF-NH2
1494	AC-YTSLIHSLIEESQNQQEKHEYELQKLDKWASLWEWF-NH2
1495	AC-YTELIHSLIEESQIQQEKKEQELQKLDKWAELWEWF-NH2
1496	AO-WQEWEQKITALLEQAQIQQEKNEYELQKLDKWEWF-NiH2
1497	AC-WQEWEQKITALLEQAQIQQEKNEYELQKLIEWASLWEWF-NH2
1498	AC-WQEWEQKITALLEQAQIQQEKNEYELQKLAKWASLWEWF-NH2
1499	AC-WQEWEQKITALLEQAQIQQEKNEYELQKLIKWASLWEWF-NH2
1600	AC-WQEWEQKITALLEQAQIQQEKNEYELQKLIEWAGLWEWF-NiH2
1601	AC-WQEWEQKITALLEQAQKQEKNEYELQKLAKWAGLWEWF-NH2
1602	AO-WQEWEQKITALLEQAQKQEKKEYELQKLIKWAGLWEWF-NH2
1603	AC-WQEWEQKITALLEQAQIQQEKNEYELQKLIEWAGLWAWF-NH2
1504	ACHIGENEORITALLEGAQIQQEKHEYELQKLAKWAGLWAWF-11H2
1605	Ac-WQEWEQKITALLEQAQIQQEKNEYELQKLIKWAGLWAWF-NH2
. 1606	Ac-WQEWEQKITALLEQAQIQQEKGEYELQKLDKWEWF-NiH2
1607	Ac-WQEWEQKITALLEQAQIQQEKGEYELLELDKWEWF-NH2
1608	Ac-WQEWEQKITALLEQAQIQQEKGEYELQKLAKWEWF-NH2
1609	Ac-WQEWEQKITALLEQAQIQQEKGEYELQKLDEWEWF-NH2
1510	AC-WQEWEQKITALLEQAQIQQEKGEYELLELAKWEWF-KH2
1611	Ac-WQEWEGKITALLEQAQIQQERIEYELLELDKWEWF-KH2
1812	AO-WOEWECKITALLEQACIQCECKEYELLELIEWASLWEWF-NH2
1013	Ao-WOEWEORTALLEDAOIQOE/GYELTELIEWAGLWEWF-Kit2
1014	AO-WOEWEOKITALLEOACHQOERNEYELLELIEWAGLWAWF-NI-12
1616	AO-WOEWEREITALLEQAQIQQEINEYELQIKLIEWASLWEWF-NH2
1616	AC-WQEWEREIQQEKNEYELQKLOKWASLWEWF-NH2
1517	Ac-WQEWEREQQEKGEYELQKLIEWEWF-NH2
1618	AO-WQEWQAQIQQEICKEYELQICLDKWASLWEWF-KIH2
1619	Ac-WQEWQAQIQQEKGEYELQKLIEWEWF-NH2

PEG-GWQEWEQRITALLEQAQIQQERNEYELQRLDEWASLWEWF-NH2 1520 Ac-GWQEWEQRITALLEQAQIQQERNEYELQRLDEWASLWEWF-NH2 1521 PEG-YTSLITALLEQAQIQQERNEQELLELDEWASLWEWF-NH2 1522 Ac-YTSLITALLEQAQIQQERNEQELLELDEWASLWEWF-NH2 1523 PEG-GWQEWEQRITALLEQAQIQQERNEYELQELDEWASLWEWF-NH2 1526 Ac-GWQEWEQRITALLEQAQIQQERNEYELQELDEWASLWEWF-NH2 1527 PEG-YTSLIGSLIEESQIQQERNEQELLELDRWASLWEWF-NH2 1528 PEG-GWQEWEQRITALLEQAQIQQERNEYELQRLDRWASLWEWF-NH2 1529 Ac-GWQEWEQRITALLEQAQIQQERNEYELQRLDRWASLWEWF-NH2 1530 PEG-GWQEWEQRITALLEQAQIQQERNEYELQELDRWASLWEWF-NH2 1531 1532 Ac-GWQEWEQRITALLEQAQIQQERNEYELQELDRWASLWEWF-NH2 PEG-YTSLIGSLIEESQNQQERNEQELLELDRWASLWNWF-NH2 1533 1534 Ac-YTSLIGSLIEESQNQQERNEQELLELDRWASLWNWF-NH2 1538 Ac-YTSLIHSLIEESQNQQEK-OH 1539 NEQELLELDK 1540 WASLWNWF-NH2 Ac-AAAWEQKITALLEQAQIQQEKNEYELQKLDKWASLWEWF-NH2 1542 1543 AC-WQEAAAKITALLEQAQIQQEKNEYELQKLDKWASLWEWF-NH2 Ac-WQEWEQAAAALLEQAQIQQEKNEYELQKLDKWASLWEWF-NH2 1544 Ac-WQEWEQKITAAAEQAQIQQEKNEYELQKLDKWASLWEWF-NH2 1545 Ac-WQEWEQKITALLAAAQIQQEKNEYELQKLDKWASLWEWF-NH2 1546 1547 Ac-WQEWEQKITALLEQAAAAQEKNEYELQKLDKWASLWEWF-NH2 Ac-WQEWEQKITALLEQAQIQAAANEYELQKLDKWASLWEWF-NH2 1548 Ac-WQEWEQKITALLEQAQIQQEKAAAELQKLDKWASLWEWF-NH2 1549 Ac-WQEWEQKITALLEQAQIQQEKNEYAAAKLDKWASLWEWF-NH2 1550 Ac-WQEWEQKITALLEQAQIQQEKNEYELQAAAKWASLWEWF-NH2 1551 1552 Ac-WQEWEQKITALLEQAQIQQEKNEYELQKLDAAASLWEWF-NH 1553 AC-WQEWEQKITALLEQAQIQQEKNEYELQKLDKWAAAAEWF-NH 1554 AC-WQEWEQKITALLEQAQIQQEKNEYELQKLDKWASLWAAA-NH 1556 Ac-YTSLIHSLIEESQNQQEKNEQELLLDKWASLWNWF-NH2 1557 Ac-YTSLIHSLIEESQNQEKNEQELLELDKWASLWNWF-NH2 1558 Ac-ERTLDFHDS-NH2 1559 Ac-YTSLIHSLIEESQNQQEKNEQELLELDKWASLWN(W)F-NH2 1563 Ac-YTSLIHSLIEESQN(Q)QEKNEQELLELDKWASLWNWF-NH2 1564 Ac-YTSLIHSLIEESQNQQDKWASLWNWF-NH2 Ac-FYEIIMDIEQNNVQGKKGIQQLQKWEDWVGWIGNI-NH2 1566 Ac-INQTIWNHGNITLGEWYNQTKDLQQKFYEIIMDIE-NH2 1567 Ac-WNHGNITLGEWYNQTKDLQQKFYEIIMDIEQNNVQ-NH2 1568 Ac-YTSLIHSLIEESENQQEKNEQELLELDKWASLWNWF-NH2 1572 Ac-YTSLIHSLIEESQDQQEKNEQELLELDKWASLWNWF-NH2 1573 Ac-YTSLIHSLIEESQNEQEKNEQELLELDKWASLWNWF-NH2 1574 c-YTSLIHSLIEESQNQEEKNEQELLELDKWASLWNWF-NH2 1575 AC-YTSLIHSLIEESQNQQEKDEQELLELDKWASLWNWF-NH2 1576 Ac-LGEWYNQTKDLQQKFYEIIMDIEQNNVQGKKGIQQ-NH2 1577 1578 Ac-WYNQTKDLQQKFYEIIMDIEQNNVQGKKGIQQLQK-NH2 1579 AC-YTSLIHSLIEESQNQQEKNEEELLELDKWASLWNWF-NH2 1580 AC-YTSLIHSLIEESQNQQEKNEQELLELDKWASLWDWF-NH2 1586 AC-XTSLIHSLIEESQNQQEKNEQELLELDKWASLWNWX-NH2 1588 AC-YNQTKDLQQKFYEIIMDIEQNNVQGKKGIQQLQKW-NH2 1598 Ac-YTSLIHSLIEESQNQQEKNEQELLELDKWASLWNWF 1600 Ac-TLTVQARQLLSGIVQQQNNLLRAIEAQQHLLQLTVWGIKQLQAR-NH2 1603 Ac-LQQKFYEIIMDIEQNNVQGKKGIQQLQKWEDWVGW-NH2 1627 Ac-YTSLIHSLIEESQNQQEKNEGELLALDKWASLWNWF-NH2 1628 AC-YTSLIHSLIEESQNQQEKNEGELLEADKWASLWWWF-NH2

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1629	AO-YTSLIHSLIEESQNQQEKNEQELLELAKWASLWNWF-NH2
1630	AC-YTSLIHSLIEESQNQQEKAEQELLELDKWASLWNWF-NH2
1631	Ac-YTSLIHSLIEESQNQQEKNAQELLELDKWASLWNWF-NH2
1632	Ac-YTSLIHSLIEESQNQQEKNEAELLELDKWASLWNWF-NH2
. 1634	Ac-WQEWEQKITALLEQAQIQQEKNEQELQKLDKWASLWEWF-NH2
1635	Ac-WQEWEQKITALLEQAQIQQEKAEYELQKLDKWASLWEWF-NH2
1636	Ac-WQEWEQKITALLEQAQIQQEKNAYELQKLDKWASLWEWF-NH2
1637	Ac-WQEWEQKITALLEQAQIQQEKNEAELQKLDKWASLWEWF-NH2
1644	Ac-EYDLRRWEK-NH2
1645	Ac-EQELLELDK-NH2
1646	Ac-EYELQKLDK-NH2
1647	Ac-WQEWEQKITALLEQAQIQQEKNEQELLKLDKWASLWEWF-NH2
1648	Ac-WQEWEQKITALLEQAQIQQEKNEQELLELDKWASLWEWF-NH2
1649	Ac-WQEWEQKITALLEQAQIQQEKNDKWASLWEWF-NH2
1650	Ac-YTSLIHSLIEESONQAEKNEQELLELDKWASLWNWF-NH2
1651	Ac-YTSUHSUEESONQQAKNEQELLELDKWASLWNWF-NH2
1652	Ac-YTSLIHSLIEESQNQQEANEQELLELDKWASLWNWF-NH2
1653	Ac-YTSLIHSLIEESANQQEANEQELLELDKWASLWNWF-NH2
1654	Ac-YTSLIHSLIEESOAQQEKNEQELLELDKWASLWNWF-NH2
	AC-YTSLIHSLIEESQNAQEKNEQELLELDKWASLWNWF-NH2
1655	AC-YTSLIHALIEESONQOEKNEQELLELDKWASLWNWF-NH2
1656	AC-YTSLIHSAIEESONOOEKNEGELLELDKWASLWNWF-NH2
1657	110 110 1111 1111 1111 1111 1111 1111 1111 1111
1658	Ac-VYPSDEYDASISQVNEEINQALAYIRKADELLENV-NH2
1659	Ac-YTSLIHSLAEESQNQQEKNEQELLELDKWASLWNWF-NH2
1660	Ac-YTSAIHSLIEESQNQQEKNEQELLELDKWASLWNWF-NH2
1661	Ac-YTSLAHSLIEESQNQQEKNEQELLELDKWASLWNWF-NH2
1662	Ac-YTSLIASLIEESQNQQEKNEQELLELDKWASLWNWF-NH2
1663	Ac-ATSLIHSLIEESQNQQEKNEQELLELDKWASLWNWF-NH2
1664	Ac-YASLIHSLIEESQNQQEKNEQELLELDKWASLWNWF-NH2
1665	Ac-YTALIHSLIEESQNQQEKNEQELLELDKWASLWNWF-NH2
1666	Ac-RIQDLEKYVEDTKIDLWSYNAELLVALENQ-NH2
1667	Ac-HTIDLTDSEMNKLFEKTRRQLREN-NH2
1668	Ac-SEMNKLFEKTRRQLREN -NH2
1669	Ac-VFPSDEADASISQVNEKINQSLAFIRKSDELLHNV-NH2
1670	Ac-VFPSDEFAASISQVNEKINQSLAFIRKSDELLHNV-NH2
1671	Ac-VFPSDEFDASISAVNEKINQSLAFIRKSDELLHNV-NH2
1672	Ac-VFPSDEFDASISQANEKINQSLAFIRKSDELLHNV-NH2
1673	Ac-VFPSDEFDASISQVAEKINQSLAFIRKSDELLHNV-NH2
1674	Ac-WQEWEQKITAALEQAQIQQEKNEYELQKLDKWASLWEWF-NH2
1675	Ac-WQEWEQKITALAEQAQIQQEKNEYELQKLDKWASLWEWF-NH2
1676	Ac-WQEWEQKITALLEQAAIQQEKNEYELQKLDKWASLWEWF-NH2
1677	Ac-WQEWEQKITALLEQAQAQQEKNEYELQKLDKWASLWEWF-NH2
1678	Ac-WQEWEQKITALLEQAQIAQEKNEYELQKLDKWASLWEWF-NH2
1679	Ac-WOEWEQKITALLEQAQIQAEKNEYELQKLDKWASLWEWF-NH2
1680	Ac-VFPSDEFDASISQVNEKINQSAAFIRKSDELLHNV-NH2
1681	Ac-VFPSDEFDASISQVNEKINQSLAAIRKSDELLHNV-NH2
1682	Ac-VFPSDEFDASISQVNEKINGSDAIRKSDEALHNV-NH2
1683	Ac-VFPSDEFDASISQVNEKINQSDAFIRKSDELAHNV-NH2
1684	Ac-VFPSDEFDASISQVNEKINQSLAFIRKSDELLANV-NH2
1685	Ac-WQEWEQKITALLEQAQIQQAKNEYELQKLDKWASLWEWF-NH2
1687	Ac-WQEWEQKITALLEQAQIQQEKNEYELQALDKWASLWEWF-NH2
1688	Ac-WQEWEQKITALLEQAQIQQEKNEYELQKADKWASLWEWF-NH2

It is to be understood that the peptides listed in Table 2 are also intended to fall within the scope of the present-invention. As discussed above, those peptides depicted in Table 2 that do not already contain enhancer peptide sequences (that is, do not represent hybrid polypeptides) can be utilized in connection with the enhancer peptide sequences and teaching provided herein to generate hybrid polypeptides. Further, the core polypeptides and the core polypeptide of the hybrid polypeptides shown in Table 2 and FIG. 13 can be used with any of the enhancer peptide sequences described herein to routinely produce additional hybrid polypeptides, which are also intended to fall within the scope of the present invention.

It is noted that while a number of the polypeptides listed in Table 2 and FIG. 13 are depicted with modified, e.g., blocked amino and/or carboxy termini or d-isomeric amino acids (denoted by residues within parentheses), it is intended that any polypeptide comprising a primary amino acid sequence as depicted to Table 2 and FIG. 13 is also intended to be part of the present invention.

The core polypeptide sequences, <u>per se</u>, shown in Table 2 and FIG. 13, as well as the hybrid polypeptides comprising such core polypeptides, can exhibit antiviral, and/or anti
fusogenic activity and/or can exhibit an ability to modulate interacellular processes that involve coiled-coil peptide structures. Among the core polypeptide sequences are, for example, ones which have been derived from individual viral protein sequences. Also among the core polypeptide sequences are, for example, ones whose amino acid sequences are derived from greater than one viral protein sequence (<u>e.g.</u>, an HIV-1, HIV-2 and SIV -derived core polypeptide).

In addition, such core polypeptides can exhibit amino acid substitutions, deletions and/or insertions as discussed, above, for enhancer polypeptide sequences as long as the particular core polypeptide's antiviral and/or antifusogenic activity (either per se or as part of a hybrid polypeptide) is not abolished.

With respect to amino acid deletions, it is preferable that the resulting core polypeptide is at least about 4-6 amino acid residues in length. With respect to amino acid insertions, preferable insertions are no greater than about 50 amino acid residues, and, more preferably no more than about 15 amino acid residues. It is also preferable that core polypeptide insertions be amino- and/or carboxy-terminal insertions.

Among such amino and/or carboxy-terminal insertions are ones which comprise amino acid sequences amino and/or carboxy to the endogenous protein sequence from which the core polypeptide is derived. For example, if the core polypeptide is derived from gp41 protein, such an insertion would comprise an amino and/or carboxy-terminal insertion comprising a gp41 amino acid sequence adjacent to the gp41 core polypeptide sequence. Such amino and/or carboxy terminal insertions can typically range from about 1, 5, 10, 15, 20, 25, 30, 35, 40, 45 or 50 amino acid residues amino to and/or carboxy to the original core polypeptide.

The hybrid polypeptides of the invention can still further comprise additional modifications that readily allow for detection of the polypeptide. For example, the hybrid polypeptides can be labeled, either directly or indirectly.

Peptide labeling techniques are well known to those of skill in the art and include, but are not limited to, radioactive, fluorescent and colorimetric techniques. Indirect labeling techniques are also well known to those of skill in the art and include, but are not limited to, biotin/streptavidin labeling and indirect antibody labeling.

The invention further relates to the association of the enhancer polypeptide sequences to types of molecules other than peptides. For example, the enhancer peptide sequences may be linked to nucleic acid molecules (e.g., DNA or RNA) or any type of small organic molecule for the purpose of enhancing the pharmacokinetic properties of said molecules.

5.2. SYNTHESIS OF PEPTIDES

The enhancer, core and hybrid polypeptides of the invention may be synthesized or prepared by techniques well known in the art. See, for example, Creighton, 1983, Proteins: Structures and Molecular Principles, W.H. Freeman ⁵ and Co., NY, which is incorporated herein by reference in its entirety. Hybrid polypeptides may be prepared using conventional step-wise solution or solid phase synthesis, fragment condensation, F-MOC or T-BOC chemistry. (see, e.g., Chemical Approaches to the Synthesis of Peptides and Proteins, Williams et al., Eds., 1997, CRC Press, Boca Raton 10 Florida, and references cited therein; Solid Phase Peptide Synthesis: A Practical Approach, Atherton & Sheppard, Eds., 1989, IRL Press, Oxford, England, and references cited therein). Likewise the amino- and/or carboxy-terminal modifications.

The enhancer, core and hybrid polypeptides of the invention can be purified by art-known techniques such as normal and reverse phase high performance liquid chromatography, ion exchange chromatography, gel electrophoresis, affinity chromatography, size exclusion, precipitation and the like. The actual conditions used to purify a particular polypeptide will depend, in part, on synthesis strategy and on factors such as net charge, hydrophobicity, hydrophilicity, solubility, stability etc., and will be apparent to those having skill in the art.

Hybrid, enhancer and core polypeptides may also be made using recombinant DNA techniques. Here, the nucleotide sequences encoding the polypeptides of the invention may be synthesized, and/or cloned, and expressed according to techniques well known to those of ordinary skill in the art. See, for example, Sambrook, et al., 1989, Molecular Cloning, A Laboratory Manual, Vols. 1-3, Cold Spring Harbor Press, NY.

One may obtain the DNA segment encoding the polypeptide of interest using a variety of molecular biological techniques, generally known to those skilled in the art. For

example, polymerase chain reaction (PCR) may be used to generate the DNA fragment encoding the protein of interest. Alternatively, the DNA fragment may be obtained from a commercial source.

The DNA encoding the polypeptides of interest may be recombinantly engineered into a variety of host vector systems that also provide for replication of the DNA in large scale. These vectors can be designed to contain the necessary elements for directing the transcription and/or translation of the DNA sequence encoding the hybrid polypeptide.

Vectors that may be used include, but are not limited to, those derived from recombinant bacteriophage DNA, plasmid DNA or cosmid DNA. For example, plasmid vectors such as pcDNA3, pBR322, pUC 19/18, pUC 118, 119 and the M13 mp series of vectors may be used. Bacteriophage vectors may include λgt10, λgt11, λgt18-23, λZAP/R and the EMBL series of bacteriophage vectors. Cosmid vectors that may be utilized include, but are not limited to, pJB8, pCV 103, pCV 107, pCV 108, pTM, pMCS, pNNL, pHSG274, COS202, COS203, pWE15, pWE16 and the charomid 9 series of vectors.

Alternatively, recombinant virus vectors including, but not limited to, those derived from viruses such as herpes virus, retroviruses, vaccinia viruses, adenoviruses, adeno-associated viruses or bovine papilloma viruses plant viruses, such as tobacco mosaic virus and baculovirus may be engineered.

In order to express a biologically active polypeptide, the nucleotide sequence coding for the protein may be inserted into an appropriate expression vector, i.e., a vector which contains the necessary elements for the transcription and translation of the inserted coding sequences. Methods which are well known to those skilled in the art can be used to construct expression vectors having the hybrid polypeptide coding sequence operatively associated with appropriate transcriptional/translational control

signals. These methods include in vitro recombinant DNA techniques and synthetic techniques. See, for example, the techniques described in Sambrook, et al., 1992, Molecular Cloning, A Laboratory Manual, Cold Spring Harbor Laboratory, N.Y. and Ausubel et al., 1989, Current Protocols in Molecular Biology, Greene Publishing Associates & Wiley Interscience, N.Y., each of which are incorporated herein by reference in its entirety.

The nucleic acid molecule encoding the hybrid, enhancer and core polypeptides of interest may be operatively 10 associated with a variety of different promoter/enhancer The promoter/enhancer elements may be selected to elements. optimize for the expression of therapeutic amounts of The expression elements of these vectors may vary in their strength and specificities. Depending on the host/vector system utilized, any one of a number of suitable 15 transcription and translation elements may be used. promoter may be in the form of the promoter which is naturally associated with the gene of interest. Alternatively, the DNA may be positioned under the control of a recombinant or heterologous promoter, i.e., a promoter that is not normally associated with that gene. For example, 20 tissue specific promoter/enhancer elements may be used to regulate the expression of the transferred DNA in specific cell types.

Examples of transcriptional control regions that exhibit tissue specificity which have been described and could be used include, but are not limited to, elastase I gene control region which is active in pancreatic acinar cells (Swift et al., 1984, Cell 38:639-646; Ornitz et al., 1986, Cold Spring Harbor Symp. Quant. Biol. 50:399-409; MacDonald, 1987, Hepatology 7:425-51S); insulin gene control region which is active in pancreatic beta cells (Hanahan, 1985, Nature 315:115-122); immunoglobulin gene control region which is active in lymphoid cells (Grosschedl et al., 1984, Cell

38:647-658; Adams et al., 1985, Nature 318:533-538; Alexander et al., 1987, Mol. Cell. Biol. 7:1436-1444): albumin gene control region which is active in liver (Pinkert et al., 1987, Genes and Devel. 1:268-276) alpha-fetoprotein gene 5 control region which is active in liver (Krumlauf et al., 1985, Mol. Cell. Biol. 5:1639-1648; Hammer et al., 1987, Science 235:53-58); alpha-1-antitrypsin gene control region which is active in liver (Kelsey et al., 1987, Genes and Devel. 1:161-171); beta-globin gene control region which is active in myeloid cells (Magram et al., 1985, Nature 315:338-10 340; Kollias et al., 1986, Cell 46:89-94); myelin basic protein gene control region which is active in oligodendrocyte cells in the brain (Readhead et al., 1987, Cell 48:703-712); myosin light chain-2 gene control region which is active in skeletal muscle (Shani, 1985, Nature 15 314:283-286); and gonadotropic releasing hormone gene control region which is active in the hypothalamus (Mason et al., 1986, Science 234:1372-1378). Promoters isolated from the genome of viruses that grow in mammalian cells, (e.g., vaccinia virus 7.5K, SV40, HSV, adenoviruses MLP, MMTV, LTR and CMV promoters) may be used, as well as promoters produced by recombinant DNA or synthetic techniques.

In some instances, the promoter elements may be constitutive or inducible promoters and can be used under the appropriate conditions to direct high level or regulated expression of the nucleotide sequence of interest. Expression of genes under the control of constitutive promoters does not require the presence of a specific substrate to induce gene expression and will occur under all conditions of cell growth. In contrast, expression of genes controlled by inducible promoters is responsive to the presence or absence of an inducing agent.

Specific initiation signals are also required for sufficient translation of inserted protein coding sequences.

These signals include the ATG initiation codon and adjacent sequences. In cases where the entire coding sequence, including the initiation codon and adjacent sequences are inserted into the appropriate expression vectors, no additional translational control signals may be needed.

- However, in cases where only a portion of the coding sequence is inserted, exogenous translational control signals, including the ATG initiation codon must be provided. Furthermore, the initiation codon must be in phase with the reading frame of the protein coding sequences to ensure translation of the entire insert. These exogenous
- translational control signals and initiation codons can be of a variety of origins, both natural and synthetic. The efficiency of expression may be enhanced by the inclusion of transcription attenuation sequences, enhancer elements, etc.

5.3. USES OF THE ENHANCER PEPTIDE SEQUENCES, CORE POLYPEPTIDES AND HYBRID POLYPEPTIDES OF THE INVENTION

As discussed above, the enhancer peptide sequences of the invention can be utilized to enhance the pharmacokinetic properties of any core polypeptide through linkage of the core polypeptide to the enhancer peptide sequences to form hybrid polypeptides. The observed enhancement of pharmacokinetic properties is relative to the pharmacokinetic properties of the core polypeptide alone. Standard pharmacokinetic character parameters and methods for determining and characterizing the pharmacokinetic properties of an agent such as a polypeptide are well known to those of skill in the art. Non-limiting examples of such methods are presented in the Examples provided below.

The enhancer peptide sequences of the invention can, additionally, be utilized to increase the in vitro or ex-vivo half-life of a core polypeptide to which enhancer peptide sequences have been attached. For example, enhancer peptide sequences can increase the half life of attached core polypeptides when the resulting hybrid polypeptides are

present in cell culture, tissue culture or patient samples, (e.g., cell samples, tissue samples biopsies, or other sample containing bodily fluids).

The core polypeptides and hybrid polypeptides of the invention can also be utilized as part of methods for

5 modulating (e.g., decreasing, inhibiting, disrupting, stabilizing or enhancing) fusogenic events. Preferably, such peptides exhibit antifusogenic or antiviral activity. The peptides of the invention can also exhibit the ability to modulate intracellular processes involving coiled-coil peptide interactions.

In particular embodiments, the hybrid polypeptides and core polypeptides of the invention that exhibit antiviral activity can be used as part of methods for decreasing viral infection. Such antiviral methods can be utilized against, for example, human retroviruses, particularly HIV (human immunodeficiency virus), e.g., HIV-1 and HIV-2, and the human T-lymphocyte viruses (HTLV-I and HTLV-II), and non-human retroviruses, such as bovine leukosis virus, feline sarcoma and leukemia viruses, simian immunodeficiency viruses (SIV), sarcoma and leukemia viruses, and sheep progress pneumonia viruses.

The antiviral methods of the invention can also be

20 utilized against non-retroviral viruses, including, but not
limited to, respiratory syncytial virus (RSV), canine
distemper virus, newcastle disease virus, human parainfluenza
virus, influenza viruses, measles viruses, Epstein-Barr
viruses, hepatitis B viruses and Mason-Pfizer viruses.

The above-recited viruses are enveloped viruses. The
antiviral methods of the invention can also be utilized
against non-enveloped viruses, including but not limited to
picornaviruses such as polio viruses, hepatitis A virus,
enterovirus, echoviruses, and coxsackie viruses,
papovaviruses such as papilloma virus, parvoviruses,
adenoviruses and reoviruses.

Other antifusogenic activities that can be modulated via methods that utilize the peptides of the invention include,

but are not limited to modulation of neurotransmitter exchange via cell fusion, and sperm-egg fusion. Among the intracellular disorders involving coiled-coil interactions that can be ameliorated via methods that utilize the peptides of the invention are disorder involving, for example, bacterial toxins.

The antifusion or antiviral activity of a given core polypeptide or hybrid polypeptide can routinely be ascertained via standard in vitro, ex vivo and animal model assays that, with respect to antiviral activity, can be specific or partially specific for the virus of interest and are well known to those of skill in the art.

The above description relates mainly to antiviral and antifusion-related activities of core and hybrid polypeptides of the invention. The hybrid polypeptides of the invention can also be utilized as part of any method for which administration or use of the core polypeptide alone might be contemplated. Use of hybrid polypeptides as part of such methods is particularly preferable in instances wherein an increase in the pharmacokinetic properties of the core polypeptide is desired. For example, insulin is utilized as part of treatment for certain types of diabetes. A hybrid polypeptide comprising an insulin or insulin fragment as the core polypeptide can, therefore, also be utilized as part of methods for ameliorating symptoms of forms of diabetes for which insulin is used and/or contemplated.

In addition to the above therapeutic methods, the peptides of the invention can still further be utilized as part of prognostic methods for preventing disorders, including, but not limited to disorders involving fusion events, intracellular processes involving coiled-coil peptides and viral infection that involves cell-cell and/or virus-cell fusion. For example, the core and hybrid polypeptides of the invention can be utilized as part of prophylactic methods of preventing viral infection.

The hybrid polypeptides of the invention can still further be utilized as part of diagnostic methods. Such

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methods can be either in vivo or in vitro methods. diagnostic method that a particular core polypeptide can be utilized can also be performed using a hybrid polypeptide comprising the core polypeptide and a modification or primary amino acid sequence that allows detection of the hybrid 5 polypeptide. Such techniques can reflect an improvement over diagnostic methods in that the increased half life of the hybrid polypeptide relative to the core polypeptide alone can increase the sensitivity of the diagnostic procedure in which it is utilized. Such diagnostic techniques include, but are not limited to imaging methods, e.g., in vivo imaging 10 methods. In a non-limiting example of an imaging method, a structure that binds the core polypeptide of a hybrid polypeptide can be detected via binding to the hybrid polypeptide and imaging (either directly or indirectly) the bound hybrid polypeptide.

5.4. PHARMACEUTICAL FORMULATIONS, DOSAGES AND MODES OF ADMINISTRATION

The peptides of the invention may be administered using techniques well known to those in the art. Preferably, agents are formulated and administered systemically. Techniques for formulation and administration may be found in ... 20 "Remington's Pharmaceutical Sciences", latest edition, Mack Publishing Co., Easton, PA. Suitable routes may include oral, rectal, vaginal, lung (e.g., by inhalation), transdermal, transmucosal, or intestinal administration; parenteral delivery, including intramuscular, subcutaneous, intramedullary injections, as well as, intrathecal, direct 25 intraventricular, intravenous, intraperitoneal, intranasal, or intraocular injections, just to name a few. For intravenous injection, the agents of the invention may be formulated in aqueous solutions, preferably in physiologically compatible buffers such as Hanks' solution, Ringer's solution, or physiological saline buffer to name a In addition, infusion pumps may be used to deliver the peptides of the invention. For transmucosal administration,

penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art.

In instances wherein intracellular administration of the peptides of the invention or other inhibitory agents is

5 preferred, techniques well known to those of ordinary skill in the art may be utilized. For example, such agents may be encapsulated into liposomes, or microspheres then administered as described above. Liposomes are spherical lipid bilayers with aqueous interiors. All molecules present in an aqueous solution at the time of liposome formation are incorporated into the aqueous interior. The liposomal contents are both protected from the external microenvironment and, because liposomes fuse with cell membranes, are effectively delivered into the cell cytoplasm. Additionally, due to their hydrophobicity, when small molecules are to be administered, direct intracellular administration may be achieved.

Nucleotide sequences encoding the peptides of the invention which are to be intracellularly administered may be expressed in cells of interest, using techniques well known to those of skill in the art. For example, expression vectors derived from viruses such as retroviruses, vaccinia viruses, adeno-associated viruses, herpes viruses, or bovine papilloma viruses, may be used for delivery and expression of such nucleotide sequences into the targeted cell population. Methods for the construction of such vectors and expression constructs are well known. See, for example, Sambrook et al., 1989, Molecular Cloning, A Laboratory Manual, Cold Spring Harbor Press, Cold Spring Harbor NY, and Ausubel et al., 1989, Current Protocols in Molecular Biology, Greene Publishing Associates and Wiley Interscience, NY.

Effective dosages of the peptides of the invention to be administered may be determined through procedures well known to those in the art which address such parameters as biological half-life, bioavailability, and toxicity. In particularly preferred embodiments, an effective hybrid

polypeptide dosage range is determined by one skilled in the art using data from routine in vitro and in vivo studies well know to those skilled in the art. For example, in vitro cell culture assays of antiviral activity, such as the exemplary assays described in Section 7, below, for T1249, will provide data from which one skilled in the art may readily determine the mean inhibitory concentration (IC) of the peptide of the polypeptide necessary to block some amount of viral infectivity (e.g., 50%, IC₅₀; or 90%, IC₉₀). Appropriate doses can then be selected by one skilled in the art using pharmacokinetic data from one or more routine animal models, such as the exemplary pharmacokinetic data described in Section 10, below, for T1249, so that a minimum plasma concentration (C_{min}) of the peptide is obtained which is equal to or exceeds the determined IC value.

Exemplary polypeptide dosages may be as low as 0.1 μ g/kg 15 body weight and as high as 10 mg/kg body weight. More preferably an effective dosage range is from $0.1 - 100 \mu g/kg$ body weight. Other exemplary dosages for peptides of the invention include 1-5 mg, 1-10 mg, 1-30 mg, 1-50 mg, 1-75 mg, 1-100 mg, 1-125 mg, 1-150 mg, 1-200 mg, or 1-250 mg of peptide. A therapeutically effective dose refers to that 20 amount of the compound sufficient to result in amelioration of symptoms or a prolongation of survival in a patient. Toxicity and therapeutic efficacy of such compounds can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, e.g., for determining the LD_{50} (the dose lethal to 50% of the population) and the ED_{50} 25 (the dose therapeutically effective in 50% of the population). The dose ratio between toxic and therapeutic effects is the therapeutic index and it can be expressed as the ratio LD₅₀/ED₅₀. Compounds which exhibit large therapeutic indices are preferred. The data obtained from these cell culture assays and animal studies can be used in 30 formulating a range of dosage for use in humans. The dosage of such compounds lies preferably within a range of

circulating concentrations that include the ED50 with little or no toxicity. The dosage may vary within this range depending upon the dosage form employed and the route of administration utilized. For any compound used in the method of the invention, the therapeutically effective dose can be $^{f 5}$ estimated initially from cell culture assays. A dose may be formulated in animal models to achieve a circulating plasma concentration range that includes the IC₅₀ (e.g., the concentration of the test compound which achieves a halfmaximal inhibition of the fusogenic event, such as a halfmaximal inhibition of viral infection relative to the amount 10 of the event in the absence of the test compound) as determined in cell culture. Such information can be used to more accurately determine useful doses in humans. Levels in plasma may be measured, for example, by high performance liquid chromatography (HPLC) or any biological or immunological assay capable of measuring peptide levels.

15 The hybrid polypeptides of the invention can be administered in a single administration, intermittently, periodically, or continuously. For example, the polypeptides of the invention can be administered in a single administration, such as a single subcutaneous, a single intravenous infusion or a single ingestion. The polypeptides 20 of the invention can also be administered in a plurality of intermittent administrations, including periodic administrations. For example, in certain embodiments the polypeptides of the invention can be administered once a week, once a day, twice a day (e.g., every 12 hours), every six hours, every four hours, every two hours, or every hour. The polypeptides of the invention may also be administered continuously, such as by a continuous subcutaneous or intravenous infusion pump or by means of a subcutaneous or other implant which allows the polypeptides to be continuously absorbed by the patient.

The hybrid polypeptides of the invention can also be administered in combination with at least one other

therapeutic agent. Although not preferred for HIV therapy, administration for other types of therapy (e.g., cancer therapy) can be performed concomitantly or sequentially, including cycling therapy (that is, administration of a first compound for a period of time, followed by administration of a second antiviral compound for a period of time and repeating this sequential administration in order to reduce the development of resistance to one of the therapies).

In the case of viral, <u>e.g.</u>, retroviral, infections, an effective amount of a hybrid polypeptide or a pharmaceutically acceptable derivative thereof can be administered in combination with at least one, preferably at least two, other antiviral agents.

Taking HIV infection as an example, such antiviral agents can include, but are not limited to DP-107 (T21), DP-178 (T20), any other core polypeptide depicted in Table 2 derived from HIV-1 or HIV-2, any other hybrid polypeptide whose core polypeptide is, at least in part, derived from HIV-1 or HIV-2, cytokines, e.g., rIFN α, rIFN β, rIFN γ; inhibitors of reverse transcriptase, including nucleoside and non-nucleoside inhibitors, e.g., AZT, 3TC, D4T, ddI, adefovir, abacavir and other dideoxynucleosides or dideoxyfluoronucleosides, or delaviridine mesylate, nevirapine, efavirenz; inhibitors of viral mRNA capping, such as ribavirin; inhibitors of HIV protease, such as ritonavir,

25 The hybrid and/or core polypeptides of the invention may, further, be utilized prophylactically for the prevention of disease. Hybrid and/or core polypeptides can act directly to prevent disease or, alternatively, can be used as vaccines, wherein the host raises antibodies against the hybrid polypeptides of the invention, which then serve to neutralize pathogenic organisms including, for example,

nelfinavir mesylate, amprenavir, saquinavir, saquinavir

mesylate, indinavir or ABT378, ABT538 or MK639; amphotericin B as a lipid-binding molecule with anti-HIV activity; and

' neutralize pathogenic organisms including, for example inhibiting viral, bacterial and parasitic infection.

For all such treatments described above, the exact formulation, route of administration and dosage can be chosen by the individual physician in view of the patient's condition. (See e.g. Fingl et al., 1975, in "The Pharmacological Basis of Therapeutics", Ch. 1 p. 1).

It should be noted that the attending physician would know how to and when to terminate, interrupt, or adjust administration due to toxicity, or to organ dysfunctions. Conversely, the attending physician would also know to adjust treatment to higher levels if the clinical response were not adequate (precluding toxicity). The magnitude of an administrated dose in the management of the oncogenic disorder of interest will vary with the severity of the condition to be treated and the route of administration. The dose and perhaps dose frequency, will also vary according to the age, body weight, and response of the individual patient. A program comparable to that discussed above may be used in veterinary medicine.

Use of pharmaceutically acceptable carriers to formulate the compounds herein disclosed for the practice of the invention into dosages suitable for systemic administration is within the scope of the invention. With proper choice of carrier and suitable manufacturing practice, the compositions 20 of the present invention, in particular, those formulated as solutions, may be administered parenterally, such as by subcutaneous injection, intravenous injection, by subcutaneous infusion or intravenous infusion, for example by The compounds can be formulated readily using pharmaceutically acceptable carriers well known in the art 25 into dosages suitable for oral administration. Such carriers enable the compounds of the invention to be formulated as tablets, pills, capsules, liquids, gels, syrups, slurries, suspensions and the like, for oral ingestion by a patient to be treated.

Pharmaceutical compositions suitable for use in the present invention include compositions wherein the active ingredients are contained in an effective amount to achieve

its intended purpose. Determination of the effective amounts is well within the capability of those skilled in the art, especially in light of the detailed disclosure provided herein.

In addition to the active ingredients, these

5 pharmaceutical compositions may contain suitable
pharmaceutically acceptable carriers comprising excipients
and auxiliaries which facilitate processing of the active
compounds into preparations which can be used
pharmaceutically. The preparations formulated for oral
administration may be in the form of tablets, dragees,

10 capsules, or solutions. For oral administration of peptides,
techniques such of those utilized by, e.g., Emisphere
Technologies well known to those of skill in the art and can
routinely be used.

The pharmaceutical compositions of the present invention may be manufactured in a manner that is itself known, <u>e.g.</u>,

by means of conventional mixing, dissolving, granulating, dragee-making, levigating, spray drying, emulsifying, encapsulating, entrapping or lyophilizing processes.

Pharmaceutical formulations for parenteral
administration include aqueous solutions of the active
compounds in water-soluble form. Additionally, emulsions and
suspensions of the active compounds may be prepared as
appropriate oily injection mixtures. Suitable lipophilic
solvents or vehicles include fatty oils such as sesame oil,
or synthetic fatty acid esters, such as ethyl oleate or
triglycerides, liposomes or other substances known in the art
for making lipid or lipophilic emulsions. Aqueous injection
suspensions may contain substances which increase the
viscosity of the suspension, such as sodium carboxymethyl
cellulose, sorbitol, or dextran. Optionally, the suspension
may also contain suitable stabilizers or agents which
increase the solubility of the compounds to allow for the
preparation of highly concentrated solutions.

Pharmaceutical preparations for oral use can be obtained by combining the active compounds with solid excipient,

optionally grinding a resulting mixture, and processing the mixture of granules, after adding suitable auxiliaries, if desired, to obtain tablets or dragee cores. Suitable excipients are, in particular, fillers such as sugars, including lactose, sucrose, trehalose, mannitol, or sorbitol; cellulose preparations such as, for example, maize starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methyl cellulose, hydroxypropylmethyl-cellulose, sodium carboxymethylcellulose, and/or polyvinylpyrrolidone (PVP). If desired, disintegrating agents may be added, such as the cross-linked polyvinyl pyrrolidone, agar, or alginic acid or a salt thereof such as sodium alginate.

Dragee cores are provided with suitable coatings. For this purpose, concentrated sugar solutions may be used, which may optionally contain gum arabic, talc, polyvinyl pyrrolidone, carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dyestuffs or pigments may be added to the tablets or dragee coatings for identification or to characterize different combinations of active compound doses.

Pharmaceutical preparations which can be used orally include push-fit capsules made of gelatin, as well as soft,

20 sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. The push-fit capsules can contain the active ingredients in admixture with filler such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active compounds may be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols. In addition, stabilizers may be added.

In instances where an enhancement of the host immune response is desired, the hybrid polypeptides may be formulated with a suitable adjuvant in order to enhance the immunological response. Such adjuvants may include, but are not limited to mineral gels such as aluminum hydroxide;

surface active substances such as lysolecithin, pluronic polyols, polyanions; other peptides; oil emulsions; and potentially useful adjuvants such as BCG and Corynebacterium parvum. Many methods may be used to introduce the vaccine formulations described here. These methods include but are not limited to oral, intradermal, intramuscular, intraperitoneal, intravenous, subcutaneous, and intranasal routes.

6. EXAMPLE: IDENTIFICATION OF CONSENSUS AMINO ACID SEQUENCES THAT COMPRISE ENHANCER PEPTIDE SEQUENCES

The retroviral gp41 protein contains structural domains referred to as the α-helix region located in the C-terminal region of the protein and the leucine zipper region located in the N-terminal region of the protein. Alignment of the enhancer peptide sequence regions contained within gp41 (FIG. 2A and 2B) of gp41 from all currently published isolate sequences of HIV-1, HIV-2 and SIV identified the consensus amino acid sequences shown in FIG. 1.

As described in detail in the Examples presented below, such sequences represent enhancer peptide sequences in that linkage of these peptide sequences to a variety of different core polypeptides enhances the pharmacokinetic properties of the resultant hybrid polypeptides.

7. EXAMPLE: HYBRID POLYPEPTIDES THAT FUNCTION AS POTENT INHIBITORS OF HIV-1 INFECTION

T1249, as depicted in FIG. 13, is a hybrid polypeptide comprising enhancer peptide sequences linked to an HIV core polypeptide. As demonstrated below, the T1249 hybrid polypeptide exhibits enhanced pharmacokinetic properties and potent in vitro activity against HIV-1, HIV-2, and SIV isolates, with enhanced activity against HIV-1 clinical isolates in HupbMC infectivity assays in vitro as well as in the HupbMC SCID mouse model of HIV-1 infection in vivo. In the biological assays described below, the activity of the

T1249 is compared to the potent anti-viral T20 polypeptide. The T20 polypeptide, also known as DP-178, is derived from HIV-1 gp41 protein sequence, and is disclosed and claimed in U.S. patent No. 5,464,933.

7.1. MATERIALS AND METHODS

7.1.1. PEPTIDE SYNTHESIS AND PURIFICATION

Peptides were synthesized using Fast Moc chemistry. Generally, unless otherwise noted, the peptides contained amidated carboxyl termini and acetylated amino termini. Purification was carried out by reverse phase HPLC.

is a 39 amino acid peptide (MW = 5036.7) composed entirely of naturally occurring amino acids and is blocked at the amino terminus by an acetyl group and the carboxyl terminus is blocked by an amido group to enhance stability. T1387 is a 23 amino acid peptide lacking enhancer peptide sequences (Ac
TALLEQAQIQQEKNEYELQKLDK-NH₂). Thus, T1387 represents the core polypeptide of the T1249 hybrid polypeptide. T1387 is blocked at its amino- and carboxy- termini in the same manner as T1249.

In particular, T1249 was synthesized using standard solid-phase synthesis techniques. The identity of the principal peak in the HPLC trace was confirmed by mass spectroscopy to be T1249.

T1249 was readily purified by reverse phase chromatography on a 6-inch column packed with a C18, 10 micron, 120A support.

25 7.1.2. <u>VIRUS</u>

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The HIV-1_{LAI} virus (Popovic, M. et al., 1984, Science 224:497-508) was propagated in CEM cells cultured in RPMI 1640 containing 10% fetal calf serum. Supernatant from the infected CEM cells was passed through a 0.2µm filter and the infectious titer estimated in a microinfectivity assay using the AA5 cell line to support virus replication. For this purpose, 20µl of serially diluted virus was added to 20µl CEM

cells at a concentration of 6 x 10⁵/ml in a 96-well microtitre plate. Each virus dilution was tested in triplicate. Cells were cultured for seven days by addition of fresh medium every other day. On day 7 post infection, supernatant samples were tested for virus replication as evidenced by reverse transcriptase activity released to the supernatant. The TCID₅₀ was calculated according to the Reed and Muench formula (Reed, L.J. et al., 1938, Am. J. Hyg. 27:493-497).

7.1.3. CELL FUSION ASSAY

- Approximately 7 x 10⁴ Molt-4 cells were incubated with 1 x 10⁴ CEM cells chronically infected with the HIV-1_{LAI} virus in 96-well tissue culture plates in a final volume of 100μ l culture medium (RPM1 1640 containing 10% heat inactivated FBS, supplemented with 1% L-glutamine and 1% Pen-Strep) as previously described (Matthews, T.J. et al., 1987, Proc.
- Natl. Acad. Sci. USA 84: 5424-5428). Peptide inhibitors were added in a volume of 10μl and the cell mixtures were incubated for 24 hr. at 37°C in 5% CO₂. At that time, multinucleated giant cells (syncytia, five cell widths or larger) were counted by microscopic examination at 10x and 40x magnification which allowed visualization of the entire
- well in a single field. Treated cells were compared to infected, untreated controls and results expressed as percent inhibition of infected controls.

7.1.4. MAGI-CCR-5 INFECTIVITY ASSAYS

- Approximately 1 x 10⁶ Magi-CCR-5 cells (obtained through the NIH AIDS Research and Reference Reagent Program, Division of AIDS, NIAID; Chackerian, B. et al., 1997, J. Virol. 71: 3932-3939) were seeded into a 48-well tissue culture plate (approximately 2 x 10⁴ cells/well in a volume of 300 μl/well selective growth medium consisting of DMEM supplemented with 10% heat inactivated FBS, 1% L-glutamine, 1% Pen/Strep,
- 30 Hygromycin B, Geneticin, and Puromycin) and allowed to attach overnight at 37°C, 5% CO₂. Cell confluency was approximately

30% by the following day. Seeding medium was removed and diluted peptide inhibitor added in volumes of 50 μ l/well (media only in untreated controls), followed by 100 μ l/well of diluted virus (desired input virus titre of 100 - 200 pfu/well). Finally, 250 μ l of selective growth medium was 5 added to each well and the plate incubated for 2 days at 37°C, 5% CO2. Fixing and staining were done according to the protocol provided by NIAID with the MAGI-CCR5 cells. Briefly, medium was removed from the plate and 500 μ l of fixative added to each well. Plates were allowed to fix for 5 minutes at room temp. Fixative was removed, each well 10 washed twice with DPBS, and 200 μ l of staining solution added to each well. The plate was then incubated at 37°C, 5% CO2, for 50 minutes, staining solution removed, and each well washed twice with DPBS. The plate was allowed to air dry before blue cells were counted by microscopic, enumerating the entire well. Treated wells were compared to infected, 15 untreated controls and results expressed as percent

7.1.5. REVERSE TRANSCRIPTASE ASSAY

inhibition of infected controls.

The micro-reverse transcriptase (RT) assay was adapted from Goff et al. (Goff, S. et al., 1981, J. Virol. 38: 239- 20 248) and Willey et al. (Willey, R. et al., 1988, J. Virol. 62: 139-147). Supernatants from virus/cell cultures were adjusted to 1% Triton-X100. 10 μ l of each supernatant/Triton X-100 sample were added to 50 ul of RT cocktail (75 mM KCl, 2 mM Clevelands reagent, 5 mM MgCl₂, 5 μ g/ml poly A, 0.25 units/ml oligo dT, 0.05% NP40, 50 mM Tris-HCl, pH 7.8, 0.5 μ M 25 non-radioactive dTTP, and 10 cCi/ml 32P-dTTP) in a 96-well Ubottom microtitre plate and incubated at 37°C for 90 min. After incubation, 40 μ l of reaction mixture from each well was transferred to a Schleicher and Schuell (S+S) dot blot apparatus, under partial vacuum, containing a gridded 96-well filter-mat (Wallac catalog #1450-423) and filter backing 30 saturated with 2x SSC buffer (0.3M NaCl and 0.003M sodium citrate). Each well was washed 4 times with at least 200 μ l

2x SSC using full vacuum. Minifold was disassembled and
gridded filter paper removed and washed 3 times with 2x SSC.
Finally, the filter membrane was drained on absorbent paper,
allowed to air dry, and sealed in heat sealable bags.
Samples were placed in a phosphorscreen cassette and an
5 erased (at least 8 min) phosphorscreen applied and closed.
Exposure was for 16 hr. Pixel Index Values (PIV), generated
in volume reporting format retrieved from phosphorimaging
(Molecular Dynamics Phosphorimager) blots, were used to
determine the affected or inhibited fraction (Fa) for all
doses of inhibitor(s) when compared to untreated, infected
controls (analyzed by ImageQuant volume report, corrected for
background).

7.1.6. HUMAN PBMC INFECTIVITY/NEUTRALIZATION ASSAY

The prototypic assay used cell lines where the primary isolate assay utilizes PBMC, obtained through Interstate Blood Bank, activated for 2-3 days with a combination of OKT3 (0.5 μg/ml) and CD28 antibodies (0.1 μg/ml). The target cells were banded on lymphocyte separation medium (LSM), washed, and frozen. Cells were thawed as required and activated as indicated above a minimum of 2-3 days prior to assay. In this 96-well format assay, cells were at a concentration of 2 x 10⁶/ml in 5% IL-2 medium and a final volume of 100 μl. Peptide stock solutions were made in DPBS (1 mg/ml). Peptide dilutions were performed in 20% FBS RPM1 1640/5% IL-2 complete medium.

7.1.7. IN VIVO HU-PBMC SCID MODEL OF HIV-1 INFECTION

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Female SCID mice (5-7 weeks old) received 5-10x10⁷ adult human PBMC injected intraperitoneally. Two weeks after reconstitution, mice were infected IP on day 0 with 10³ TCID₅₀ HIV-1 9320 (AZT-sensitive isolate A018). Treatment with peptides was IP, bid, beginning day -1 and continuing through day 6. The extent of infection in blood cells, splenocytes,

lymph nodes, and peritoneal cells was assayed by quantitative co-culture with human PBMC blasts weekly for three consecutive weeks following animal exsanguinations and tissue harvest (day 7, approximately 12-18 hours following the last drug treatment). Co-culture supernatants were evaluated for HIV-1 p24 antigen production as a measure of virus infection (Immunotek Coulter kits and protocol).

7.1.8. RAT PHARMACOKINETIC STUDIES

250-300 g male CD rats, double jugular catheter, obtained from Charles River Laboratories were used. Peptides were injected in one jugular catheter in a volume of 200 μl of peptide solution (approximately 3.75 mg/ml), dosing solution concentration was determined using the Edelhoch method, (Edelhoch, 1967, Biochemistry 6:1948-1954) method and adjusted based on animal weight such that each animal received a dose of 2.5 mg/kg). Approximately 250-300 μl of blood was removed at predetermined time intervals (0, 15, 30 min and 1, 2, 4, 6, and 8 hours) and added to EDTA capiject tubes. Plasma was removed from pelleted cells upon centrifugation and either frozen or immediately processed for fluorescence HPLC analysis.

7.1.9. FLUORESCENCE HPLC ANALYSIS OF PLASMA SAMPLES

100 μl of sample plasma was added to 900 μl of precipitation buffer (acetonitrile, 1.0% TFA, detergent) resulting in precipitation of the majority of plasma proteins. Following centrifugation at 10,000 rpm for 10 min, 400 μl of the supernatant was removed and added to 600 μl of HPLC grade water. Serial dilutions were performed as dictated by concentration of peptide present in each sample in dilution buffer comprised of 40% precipitation buffer and 60% HPLC water. In addition to sample dilutions, serial dilutions of dosing solution were performed in buffer as well as in plasma and used to generate a standard curve relating peak area to known concentration of peptide. This curve was

then used to calculate concentration of peptide in plasma taking into account all dilutions performed and quantity injected onto column.

7.1.10. XTT PROTOCOL

In order to measure cytotoxic/cytostatic effects of 5 peptides, XTT assays (Weislow, O.S. et al., 1989, J. Natl. Cancer Inst. 81:577-586) were performed in the presence of varying concentrations of peptide in order to effectively establish a selective index (SI). A TC₅₀ was determined in this assay by incubating cells in the presence and absence of 10 serially diluted peptide followed by the addition of XTT. surviving/metabolizing cells XTT is reduced to a soluble brown dye, XTT-formazan. Absorbance is read and comparisons made between readings in the presence and absence of peptide to determine a TC₅₀ utilizing the Karber method (see. e.g., Lennette, E.H. et al., eds., 1969, "Diagnostic Procedures for 15 Viral and Rickettsial Infections," American Public Health Association, Inc., fourth ed., pp. 47-52). Molt 4, CEM (80,000 cells/well) and a combination of the two cell types (70,000 and 10,000 respectively) were plated and incubated with serially diluted peptide for 24 hours in a total volume of 100 μ l. Following incubation, 25 μ l of XTT working stock 20 (1 mg/ml XTT, 250 μ M PMS in complete medium containing 5% DMSO) was added to each well and the plates incubated at 37°C. Color development was read and results used to express values generated from peptide containing wells as a percentage of the untreated control wells.

25

7.2. RESULTS

7.2.1. ANTIVIRAL ACTIVITY - FUSION ASSAYS

T1249 was directly compared to T20 in virus mediated cell-cell fusion assays conducted using chronically infected CEM cells mixed with uninfected Molt-4 cells, as shown in Table 3, below. T1249 fusion inhibition against lab isolates such as IIIb, MN, and RF is comparable to T20, and displays

an approximately 2.5-5-fold improvement over T20. T1249 was also more active (3-28 fold improvement) than T20 against several syncytia-inducing clinical isolates, including an AZT resistant isolate (G691-2), a pre-AZT treatment isolate (G762-3), and 9320 (isolate used in HuPBMC-SCID studies).

Most notably, T1249 was over 800-fold more potent than T20 against HIV-2 NIHZ.

TABLE 3

10	Virus Isolate	T20 (ng/ml)	n	T1249 (ng/ml)	n	Fold Differenc e
ĺ	HIV-1 IIIb	2.5	9	1.0	9	2.5
	HIV-1 G691-2 (AZT-R)	406.0	, 1	16.0	1	25
	HIV-1 G762-3 (Pre- AZT)	340.1	1	12.2	1	28
	HIV-1 MN	20.0	. 7	3.1	7	6
15	HIV-1 RF	6.1	7	2.1	7	3
	HIV-1 9320	118.4	1	34.5	1	3
	HIV-2 NIHZ	3610.0	>10	4.3	2	840

7.2.2. ANTIVIRAL ACTIVITY - Magi-CCR-5 INFECTIVITY ASSAYS

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Magi-CCR-5 infectivity assays allow direct comparisons to be made of syncytia and non-syncytia inducing virus isolates, as well as comparisons between laboratory and clinical isolates. The assay is also a direct measure of virus infection (TAT expression following infection,

25 transactivating an LTR driven beta-galactosidase production), as opposed to commonly used indirect measures of infectivity such as p24 antigen or reverse transcriptase production.

Magi-CCR-5 infectivity assays (see Table 4 below) reveal that T1249 is consistently more effective than T20 against all isolates tested, in terms of both EC50 and Vn/Vo = 0.1

30 inhibition calculations. T1249 shows considerable improvement in potency against the clinical isolate HIV-1

301714 (>25-fold), which is one of the least sensitive isolates to T20. In addition, T1249 is at least 100-fold more potent than T20 against the SIV isolate B670. These data, along with fusion data suggest that T1249 is a potent peptide inhibitor of HIV-1, HIV-2, and SIV.

5

TABLE 4

		T20		T1249		
Virus Isolate	EC-50	Vn/Vo=0.1	E C- 50	Vn/Vo=0.1	EC-50 Fold Difference	Vn/Vo=0.1 Fold Difference
HIV-1 IIIB	42	80	8	10	5	8
HIV-1 9320	11	50	1	6	11	8
HIV-1 301714 (subtype B, NSI)	1065	4000	43	105	25	38
HIV-1 G691-2 (AZT-R)	13	200	0. 3	20	43	10
HIV-1 pNL4-3	166	210	1	13	166	16
SIV-B670	2313	>10000	21	100	110	>100

7.2.3. ANTIVIRAL ACTIVITY - HUPBMC INFECTIVITY ASSAYS

assays (Table 5, below), which represent a recognized surrogate in vitro system to predict plasma drug concentrations required for viral inhibition in vivo. These comparisons revealed that T1249 is more potent against all HIV-1 isolates tested to date, with all Vn/Vo = 0.1 (dose required to reduce virus titer by one log) values being reduced to sub-microgram concentrations. Many of the least

sensitive clinical isolates to T20 exhibited 10-fold or greater sensitivity to T1249. It is noteworthy that HIV-1 9320, the isolate used in the HuPBMC SCID mouse model of infection, is 46-fold less sensitive to T20 than to T1249, indicating a very good correlation with the *in vivo* results.

5

TABLE 5

	·	T20	T1249	
	Virus Isolate (HIV-1)	Vn/Vo = 0.1 (ng/ml)	Vn/Vo = 0.1 (ng/ml)	Fold Difference
0	IIIB	250	80	3
	9320	6000	130	46
	301714 (subtype B, NSI)	8000	700	11
	302056 (subtype B, NSI)	800	90	9
5	301593 (subtype B, SI)	3500	200	18
	302077 (subtype A)	3300	230	14
	302143 (SI)	1600	220	7
	G691-2 (AZT-R)	1300	400	3

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7.2.4. ANTIVIRAL ACTIVITY - T20 RESISTANT <u>LAB</u> ISOLATES

T1249 was directly compared to T20 in virus mediated cell-cell fusion assays conducted using chronically infected CEM cells mixed with uninfected Molt-4 cells (Table 6, below). T1249 was nearly 200-fold more potent than T20 against a T20-resistant isolate.

TABLE 6

Virus Isolate	T20 (ng/ml)	n	T1249 (ng/ml)	n	Fold Difference
HIV-1 pNL4-3 SM (T20 Resistant)	405.3	3	2.1	3	.193

In Magi-CCR-5 assays (see Table 7, below), T1249 is as much as 50,000-fold more potent than T20 against T20-resistant isolates such as pNL4-3 SM and pNL4-3 STM (Rimsky, L. and Matthews, T., 1998, J. Virol. 72:986-993).

5

TABLE 7

			T20		T1249		
	Virus Isolate (HIV-1)	EC- 50	Vn/Vo = 0.1	EC-50	Vn/Vo=0.1	EC-50 Fold Difference	Vn/Vo=0.1 Fold Difference
0	pNL4-3	166	210	1	13	166	16
	pNL4-3 SM (T20-R)	90	900	4	11	23	82
	pNL4-3 SM (T20-R) Duke	410	2600	4	11	103	236
5	pNL4-3 STM (T20/T649- R)	>50 000	>5000 0	1	13	>50000	>3846

T1249 was directly compared to T20 in HuPBMC infectivity

assays (see Table 8, below), evaluating differences in potency against a resistant isolate. T1249 is greater than 250-fold more potent than T20 against the resistant isolate pNL4-3 SM.

TABLE 8

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	T20	T1249	
Virus Isolate (HIV-1)	Vn/Vo = 0.1 (ng/ml)	Vn/Vo = 0.1 (ng/ml)	Fold Difference
pNL4-3	3500	30	117
pNL4-3 SM (T20-R)	>10000	40	>250

7.2.5. ANTIVIRAL ACTIVITY - IN VIVO SCID-HUPBMC MODEL

In vivo antiviral activity of T1249 was directly compared to T20 activity in the HuPBMC-SCID mouse model of HIV-1 9320 infection (FIG. 3). Two weeks after 5 reconstitution with HuPBMCs, mice were infected IP on day 0 with 103 TCID50 HIV-1 9320 passed in PBMCs (AZT-sensitive isolate A018). Treatment with peptides was IP, bid, for total daily doses of 67 mg/kg (T20), 20 mg/kg (T1249), 6.7 mg/kg (T1249), 2.0 mg/kg (T1249), and 0.67 mg/kg (T1249), for 8 days beginning on day -1. The extent of infection in blood 10 cells, splenocytes, lymph nodes, and peritoneal cells was assayed by quantitative co-culture with human PBMC blasts weekly for three consecutive weeks following animal exsanguinations and tissue harvest (day 7, approx. 12 to 18 hours following last drug treatment). Co-culture supernatants were evaluated for HIV-1 p24 antigen production 15 as a measure of virus infection. Infectious virus was not detectable in the blood or lymph tissues of the T20-treated animals, although, virus was detected in the peritoneal washes and spleen preparation. All compartments were negative for infectious virus at the 6.7 mg/kg dose of T1249, indicating at least a 10-fold improvement over T20 treatment. 20 At the 2.0 mg/kg dose of T1249, both the lymph and the spleen were completely free of detectable infectious virus, with a 2 log10 reduction in virus titer in the peritoneal wash and a 1 log₁₀ reduction in virus titer in the blood, compared to infected controls. At the lowest dose of T1249, 0.67 mg/kg, the peritoneal washes and blood were equivalent to infected 25 control; however, at least a 1 log₁₀ drop in infectious virus titer was observed in both the lymph and the spleen tissues. Overall, the results indicate that T1249 is between 30 and 100-fold more potent against HIV-1 9320, in vivo, under these

conditions.

7.2.6. PHARMACOKINETIC STUDIES - RAT

Cannulated rats were used to further define the pharmacokinetic profile of T1249. Male CD rats, 250-300 g, were dosed IV through a jugular catheter with T1249 and T20 (FIGS. 4A-5). The resulting plasma samples were evaluated using fluorescence HPLC to estimate peptide quantities in extracted plasma. The beta-phase half-life and total AUC of T1249 was nearly three times greater than T20 (FIG. 5).

7.2.7. CYTOTOXICITY

No overt evidence of T1249 cytotoxicity has been observed in vitro, as demonstrated in FIG. 6.

In addition, T1249 is not acutely toxic (death within 24 hours) at 167 mg/kg (highest dose tested) given IV through jugular cannula (0.3 ml over 2-3 min).

7.2.8. DIRECT BINDING TO gp41 CONSTRUCT M41 \(\Lambda \) 178

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T1249 was radiolabelled with ¹²⁵I and HPLC- purified to maximum specific activity. T20 was iodinated in the same manner. Saturation binding of to M41Δ178 (a truncated gp41 ectodomain fusion protein lacking the T20 amino acid sequence) immobilized on microtitre plates at 0.5 mg/μl is shown in FIG.7. Nonspecific binding was defined as binding of the radioligand in the presence of 1 μM unlabeled peptide. Specific binding was the difference between total and nonspecific binding. The results demonstrate that ¹²⁵I-T1249 and ¹²⁵I-T20 have similar binding affinities of 1-2 nM. Linear inverse Scatchard plots suggests that each ligand binds to a homogeneous class of sites.

The kinetics of ¹²⁵I-T1249 and ¹²⁵I-T20 binding was determined on scintillating microtitre plates coated with 0.5 μg/ml M41Δ178. The time course for association and dissociation is shown in FIG.8. Dissociation of bound radioligand was measured following the addition of unlabeled peptide to a final concentration of 10 μM in one-tenth of the total assay volume. Initial on- and off-rates for ¹²⁵I-T1249

were significantly slower than those of ¹²⁵I-T20.

Dissociation patterns for both radioligands were unchanged - when dissociation was initiated with the other unlabeled peptide (i.e., ¹²⁵I-T1249 with T20).

To further demonstrate that both ligands compete for the same target site, unlabeled TI249 and T20 were titrated in the presence of a single concentration of either ¹²⁵I-T1249 or ¹²⁵I-T20. Ligand was added just after the unlabeled peptide to start the incubation. The competition curves shown in FIG.9 suggest that although both ligands have similar affinities, a higher concentration of either unlabeled T20 or T1249 is required to fully compete for bound ¹²⁵I-T1249.

7.2.9. DIRECT BINDING TO THE HR1 REGION OF GP41

Circular dichroism (CD) spectroscopy was used to measure the secondary structure of T1249 in solution (phosphatebuffered saline, pH 7) alone and in combination with a 45residue peptide (T1346) from the HR1 (heptad repeat 1) binding region of gp 41. FIG. 14A illustrates the CD spectrum of T1249 alone in solution (10 μ M, 1 $^{\circ}$ C). spectrum is typical of peptides which adopt an alpha-helical structure. In particular, deconvolution of this spectrum 20 using single value decomposition with a basis set of 33 protein spectra predicts the helix content of T1249 (alone in solution) to be 50%. FIG. 14B illustrates a representative CD spectrum of T1249 mixed with T1346. The closed squares (■) represent a theoretical CD spectrum predicted for a "non-interaction model" wherein the peptides are hypothesized 25 to not interact in solution. The actual experimental spectrum (●) differs markedly from this theoretical "noninteraction model" spectrum, demonstrating that the two peptides do, indeed, interact, producing a measurable structural change which is observed in the CD spectrum.

7.2.10. PROTEASE PROTECTION OF THE T1249 BINDING REGION WITHIN GP41

The susceptibility of the chimeric protein M41A178, described in Section 7.2.8 above, to proteinase-K digestion was determined and analyzed by polyacrylamide gel electrophoresis. The results are illustrated in FIG. 15.

When either M41\(\text{1178}\) (untreated; FIG 15, lane 2) or T1249 (untreated; FIG. 15, lane 4) are incubated individually with proteinase K (FIG. 15, lanes 3 and 5, respectively), both are digested. However, when T1249 is incubated with M41\(\text{\text{1178}}\) prior to addition of proteinase-K

10 (FIG. 15, lane 7), a protected HR-1 fragment of approximately 6500 Daltons results. Sequencing of the protected fragment demonstrates that it corresponds to a region of primary sequence located within the ectodomain of gp41. The protected fragment encompasses the soluble HR1 peptide (T1346) used in the CD studies described in Section 7.2.9

15 above, and further contains an additional seven amino acid residues located on the amino terminus. This protection can be attributed to the binding of T1249 to a specific sequence of gp41 which is contained in the M41\(\text{\text{178}}\) construct.

8. EXAMPLE: RESPIRATORY SYNCYTIAL VIRUS HYBRID POLYPEPTIDES

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The following example describes respiratory syncytial virus (RSV) hybrid polypeptides with enhanced pharmacokinetic properties. In addition, results are presented, below, which demonstrate that the RSV hybrid polypeptides represent potent inhibitors of RSV infection.

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8.1. MATERIALS AND METHODS

8.1.1. PEPTIDE-SYNTHESIS AND PURIFICATION

RSV polypeptides were synthesized using standard Fast Moc chemistry. Generally, unless otherwise noted, the peptides contained amidated carboxyl termini and acetylated amino termini. Purification was carried out by reverse phase HPLC.

8.1.2. RESPIRATORY SYNCYTIAL VIRUS PLAQUE REDUCTION ASSAY

All necessary dilutions of peptides were performed in clean, sterile 96-well TC plate. A total of eleven dilutions for each peptide and one control well containing no peptide were assembled. The final concentration range of peptide started at 50µg/ml or 100µg/ml, with a total of eleven two-fold dilutions. The RSV was prepared at a concentration of 100PFU/well in 100µl 3% EMEM, as determined by a known titer of RSV. The virus is then added to all of the wells.

The media was removed from one sub-confluent 96-well

10 plate of Hep2 cells. The material from the dilution plate
was transferred onto the cell plates starting with row 1 and
then transferring row 12, row 11, etc. until all rows were
transferred. Plates were placed back into the incubator for
48 hours.

The cells were checked to ensure that syncytia were present in the control wells. Media was removed and approximately 50 μ ls of 0.25% Crystal Violet in methanol was added to each well. The wells were rinsed immediately in water to remove excess stain and allowed to dry. Using a dissecting microscope, the number of syncytia in each well was counted.

20

8.2. RESULTS

Pharmacokinetic studies with the RSV hybrid peptides T1301 (Ac-WQEWDEYDASISQVNEKINQALAYIREADELWA WF-NH₂) and T1302 (Ac-WQAWDEYDASISQVNEKINQALAYIREADELW AWF-NH₂) containing enhancer peptide sequences demonstrated a greatly enhanced half-life relative to core peptide T786 (Ac-VYPSDEYDASISQVNEEINQALAYIRKADELLENV-NH₂), as demonstrated in FIG. 10A-10B. Hybrid polypeptides T1301, T1302 and T1303 (Ac-WQAWDEYDASISDVNEKINQALAYIREADELWEWF-NH₂) also showed a greatly enhanced half-size relative to core peptide T1476 (Ac-DEYDASISQVNEKINQALAYIREADEL-NH₂).

RSV hybrid polypeptides T1301, T1302 and T1303, as well as polypeptide T786 and T1293, were tested for their ability

to inhibit RSV plaque formation of HEp2 cells. As indicated in FIGS. 11A and 11B, both the tested hybrid RSV polypeptides, as well as the T786 core polypeptide were able to inhibit RSV infection. Surprisingly, the T1293 hybrid polypeptide was also revealed to be a potent anti-RSV compound (FIG. 13).

9. EXAMPLE: LUTEINIZING HORMONE HYBRID POLYPEPTIDES

The example presented herein describes luteinizing hormone (LH) hybrid proteins with enhanced pharmacokinetic

10 properties. The following LH hybrid peptides were synthesized and purified using the methods described above: core peptide T1323 (Ac-QHWSYGLRPG-NH2) and hybrid polypeptide T1324 (Ac-WQEWEQKIQHWSYGLRPGWASLWEWF-NH2) which comprises the core polypeptide T1323 amino acid sequence coupled with enhancer peptides at its amino- and carboxy-termini. As

15 demonstrated in FIG. 12A and 12B, the T1324 hybrid peptide exhibited a significantly increased half-life when compared to the T1323 core peptide which lacks the enhancer peptide sequences.

10. EXAMPLE: PHARMACOLOGY OF HYBRID POLYPEPTIDE T1249

T1249, depicted in FIG. 13, is a hybrid polypeptide comprising enhancer peptide sequences linked to a core polypeptide derived from a mix of viral sequences. As demonstrated in the Example presented in Section 7 above, the T1249 hybrid polypeptide exhibits enhanced pharmacokinetic properties and potent in vitro as well as in vivo activity against HIV-1. In the example presented below, the pharmacological properties of T1249 in both rodent and primate animal models are further described.

10.1. MATERIALS AND METHODS

10.1.1. SINGLE-DOSE ADMINISTRATION TO RODENTS

T1249 was administered to Sprague-Dawley albino rats in a single dose administered by continuous subcutaneous infusion (SCI), subcutaneous (SC) injection or intravenous 5 (IV) injection. Each treatment group consisted of nine rats per sex per group. The groups received sterile preparations of T1249 bulk drug substance at a dose of 0.5, 2.0, or 6.5 mg/kg by CSI. One group received 50mM carbonatebicarbonate, pH 8.5, administered as a control. The peptides were given for 12 hours via a polyvinyl chloride/polyethylene 10 catheter surgically implanted subcutaneously in the nape of the neck. Two groups received a single dose of T1249 at a dose of 1.2 or 1.5 mg/kg by subcutaneous injection into the intrascapular region. Two groups received a single dose of T1249 at a dose of 1.5 or 5 mg/kg via intravenous injection. The actual milligram amount of T1249 was calculated using the 15 peptide content that was determined for the batch administrated.

Endpoints for analysis included cageside observations (twice daily for mortality and moribundity), clinical observations, clinical laboratory parameters, body weight and necropsy. Blood samples were obtained by a sparse sampling technique over a 12 hour time period from three rats per sex per group at each of the following times: 0.5, 1, 2, 4, 6, 8, 19, and 12 hours after dose administration. Sample analysis was performed using a PcAb ECLIA assay (Blackburn, G. et al., 1991, Clin. Chem. 37:1534-1539; Deaver, D., 1995, Nature 377:758).

For plasma and lymphatic pharmacokinetic analysis of T1249 in rats, T1249 was prepared as a sterile solution in bicarbonate buffer and administered as a single dose, bolus intravenous injection into the lateral tail vain at a dose of 20 mg/kg. Blood was collected from the animal from an indwelling jugular catheter. Samples were collected

immediately after dosing and at 5, 15, and 30 minutes, and 1, 2, 4, and 6 hours after drug administration. For the

analysis of lymphatic fluids, samples were taken immediately before dosing and every 20 minutes for the first six hours after dosing. Lymphatic fluid was collected from a catheter placed directly into the thoracic lymphacic duct as previously described (Kirkpatrick and Silver, 1970, The Journal of Surgical Research 10:147-158). The concentrations of T1249 in plasma and lymphatic fluid were determined using a standard T1249 Competitive ELISA assay (Hamilton, G. 1991, p. 139, in "Immunochemistry of Solid-Phase Immunoassay,", Butler, J., ed., CRC Press, Boston).

10

10.1.2. SINGLE-DOSE ADMINISTRATION TO PRIMATES

Sterile preparations of T1249 bulk drug substance were administered to cynomolgus monkeys in single doses administered by subcutaneous (SC), intramuscular (IM) or intravenous (IV) injection. In a sequential crossover design, one group of animals consisting of two per sex received a single bolus dose of T1249 by IV (0.8 mg/kg), IM (0.8 mg/kg) or SC (0.4, 0.8, and 1.6 mg/kg) injection. A washout period of at least three days separated each dosing day. Lyophilized T1249 was reconstituted in sterile phosphate buffered saline pH 7.4 immediately prior to dosing. The actual milligram amount of test article was calculated using the peptide content that was determined for the batch administered.

Endpoints for analysis included cageside observations, physical examinations and body weight. For the IV phase of the study, blood samples were collected into heparinized tubes at the following time points: immediately after dosing, 0.25, 0.5, 1.5, 3, 6, 12, and 24 hours after dosing. For the IM and SC phases of the study blood samples were collected in heparinized tubes from each animal at the following time points: 0.5, 1, 2, 3, 6, 12, and 24 hours after dosing. Plasma samples were prepared within one hour of collection and flash frozen in liquid nitrogen. Samples analysis was performed using a PCAb ECLIA assay (Blackburn,

G. et al., 1991, Clin. Chem. <u>37</u>:1534-1539; Deaver, D., 1995; Nature <u>377</u>:758).

10.1.3. BRIDGING PHARMACOKINETIC STUDY

Six male cynomolgus monkeys were randomly assigned to

three groups consisting of two animals per group. All doses
of T1249 were given by bolus subcutaneous injection. The
study was divided into two sessions. In Session 1, animals
in groups 1, 2 and 3 received a sterile preparation of T1249
bulk drug substance (i.e., bulk +1249 dissolved in carbonatebicarbonate, pH 8.5) twice daily for four consecutive days

(Study Days 1-4) at doses of 0.2, 0.6 and 2.0 mg/kg/dose,
respectively. A ten day washout period separated Session 1
and Session 2. In Session 2, animals in groups 1, 2, and 3
received a sterile preparation of T1249 drug product (i.e.,
in aqueous solution, pH 6.5, plus mannitol) twice daily for
four consecutive days (Study Days 15-18) at doses of 0.2, 0.6
and 2.0 mg/kg/dose, respectively.

Blood samples for pharmacokinetic analyses were collected on Study Days 1 and 15 to assess single-dose pharmacokinetic parameters, and on Study Days 4 and 18 to assess steady-state plasma pharmacokinetic parameters. Samples were collected at the following times: immediately pre-dose, and 0.5, 1.5, 3.0, 4.0, 6.0, 8.0 and 12.0 hours post-dose. Animals were monitored during Sessions 1 and 2 for clinical signs and changes in body weight.

10.2. RESULTS

10.2.1. PHARMACOKINETICS OF T1249 ADMINISTERED TO RATS

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Rat models were used to perform an initial assessment of plasma pharmacokinetics and distribution of T1249. For animals in all dose groups, there were no changes in body weight, physical observations, hematology and clinical chemistry parameters or macroscopic pathology observations related to the administration of T1249.

Rats that received T1249 by CSI achieved steady-state plasma peptide concentrations approximately four hours after administration. Both the steady-state concentration in plasma (Cp_{ss}) and calculated area under the plasma concentration versus time curve (AUC) were directly proportional to the administered dose, indicating that T1249 displays linear pharmacokinetics within the tested dose range of 0.5 to 6.5 mg/kg. Both the calculated pharmacokinetic parameters and the plasma concentration versus time curves for the CSI route of administration are presented in Table 9 and in FIG. 16A, respectively.

10

TABLE 9

		`	Dose Groups	
	Parameter	0.5 mg/kg	2.0 mg/kg	6.5 mg/kg
	Cp _{ss} (μg/ml)	0.80	2.80	10.9
5	$AUC_{(0-12h)}$ ($\mu g \cdot h/ml$)	7.99	25.9	120

15

Administration of T1249 by bolus IV injection resulted in linear dose-dependent pharmacokinetics within the doses tested. In contrast, exposure to T1249 by SC injection was not dose-dependent within the dose range studied. The calculated pharmacokinetic parameters and plasma concentration versus time curves for both SC and IV administration of T1249 are shown in Table 10 and FIG. 16B respectively.

25

TABLE 10

	D	ose Groups/1	Administratio	n		
Parameter	(8	(C)	(IV)			
	1.2 mg/kg	15 mg/kg	1.5 mg/kg	5.0 mg/kg		
t _{1/2, terminal} (hours)	2.02	2.00	2.46	1.86		

 t_{max} (hours) 1.09 1.88 - - - C_{max} (μ g/ml) 6.37 21.5 15.7 46.3 - AUC_(0-12h) 27.0 107 45.6 118

PCT/US99/11219

(μg•h/ml)
5 AUC₍₀₋₋₎ 27.6 110 47.1 120 (μg•h/ml)

TABLE 11

WO 99/59615

15

	Route	Dose	AUC (0)	Normalized AUC(0-	$\mathbf{F}_{\mathbf{R}}$
		(mg/kg)	(μg•h/ml)	~) (μg•h/ml)	(%)
-	Low Dose				
	sc	1.2	27.6	34.5 ^(a)	73
	IV	1.5	47.1	-	-
	High Dose				
	sc	15	110	36.5 ^(b)	30
	ıv	5	120	-	-

25 Normalized from a 1.2 mg/kg dose to a 1.5 mg/kg dose by multiplying AUC(0-1) by 1.25.

(b) Normalized from a 15 mg/kg dose to a 5 mg/kg dose by dividing AUC $_{(0-s)}$ by 3.

The kinetic data for both plasma and lymph concentrations of T1249 are illustrated in FIG. 16C and tabulated below in Table 12. T1249 rapidly penetrated into the lymphatic system and equilibrated with the plasma reservoir of drug within approximately one hour after

administration. Following equilibration between the two compartments, plasma and lymph levels of drug were comparable out to three hours post-dosing in four out of five animals. One animal had consistently lower concentrations of T1249 in the lymph than the other animals, however this animal's lymph 5 elimination profile was indistinguishable from other members of the group. Comparison of the elimination phase half-life (t1/2) for plasma and lymph suggest that the transit of T1249 between these two compartments is a diffusion-controlled process. After three hours, there appeared to be a second, more rapid elimination phase from the lymphatic system. 10 difference could be mechanism-based (e.g., due to redistribution or accelerated peptide degradation in the lymph) or due to other factors. The concentration of T1249 in lymphatic fluid six hours post-injection is greater than the IC90 for viral infectivity for common laboratory strains and for primary clinical isolates of HIV-1. 15

The extent of penetration of T1249 into cerebrospinal fluid (CSF) was also assessed. T1249 concentrations were below the limit of detection (LOD; 2.0 ng T1249/ml CSF) at all measurable time points, indicating that T1249 does not penetrate the central nervous system after a single dose administration.

20

TABLE 12

	T1249					
Parameter	Plasma	Lymph				
t _{1/2} , elimination(hours)	2.6±0.41	1.3±0.27				
C_{max} (μ g/ml)	291	133 ^(a) /155 ^(b)				
$AUC_{(0-6h)}$ ($\mu g \cdot h/ml$)	506	348 ^(a) /411 ^(b)				
$AUC_{(0-\infty)}$ ($\mu g \bullet h/ml$)	598	390 ^(a) /449 ^(b)				
Cl (ml/h)	7.8	11.5				

(a) Calculated averages include one animal (Rat #1) that exhibited significantly lower lymph concentrations but a similar kinetic profile by comparison to the other animals in the group.

(b) Calculated averages that exclude Rat #1.

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10.2.2. PHARMACOKINETICS OF T1249 ADMINISTERED TO PRIMATES

Primate models were used to evaluate the relationship between dose level and various pharmacokinetic parameters associated with the parenteral administration of T1249. Plasma concentrations greater than 6.0 μ g/ml of T1249 were achieved by all routes of administration and quantifiable levels (i.e., levels greater than 0.5 μ g/ml) were detected at 24 hours after SC and IV administration. The elimination $t_{1/2}$ was comparable for all routes of administration (5.4 hours, 4.8 hours and 5.6 hours for IV, SC and IM administration, respectively). Plasma concentrations of T1249 that exceed the IC₉₀ values for laboratory strains and clinical isolates of HIV-1 were observed at all measured time points throughout the 24 hour sampling period.

A comparison of the data obtained for the parenteral administration of 0.8 mg/kg T1249 via all routes of administration (SC, IV, and IM) is presented in FIG. 17A. FIG. 15B illustrates a comparison of the data obtained from SC injection at three different dose levels of T1249 (0.4 mg/kg, 0.8 mg/kg, and 1.6 mg/kg). The insert in FIG. 17B contains a plot of the calculated AUC versus administered dose.

T1249 displays linear pharmacokinetics in cynomolgus monkeys following SC administration within the range of administered doses, indicating that saturation of the clearance mechanism or mechanisms has not occurred within this range. A summary of the pharmacokinetic data following parenteral administration of T1249 to cynomolgus monkeys is provided in Table 13, below. A comparison of the plasma AUC values indicates that, relative to intravenous administration, the bioavailability of T1249 is approximately

64% when given by intramuscular injection and 92% when given by subcutaneous injection.

Table 13

5				Double (Do	an Inval	ma /ka\	
	Parameter	Admini	4.83±0.48 5.55±0.92 5.57±0.24 5.35±0.9 4.58±1.45 4.72±1.81 2.32±0.43 - 6.85±1.01 13.3±2.55 6.37±1.69 26.7±0.2 8.12±11.4 168±34.0 56.4±12.3 87.4±25. 85.3±13.6 181±44.0 59.5±13.1 92.5±25.	mg/kg/			
		sc (0.4)	SC (0.8)	SC (1.6)	IM (0.8)	IV (0.8)	
	t _{1/2, terminal} (h)	6.23±0.52	4.83±0.48	5.55±0.92	5.57±0.24	5.35±0.95	
	t _{max} (h)	3.97±1.18	4.58±1.45	4.72±1.81	2.32±0.43	-	
	C_{max} ($\mu g/ml$)	3.17±0.09	6.85±1.01	13.3±2.55	6.37±1.69	26.7±0.25	
LO	AUC (0-24)	37.5±6.6	8.12±11.4	168±34.0	56.4±12.3	87.4±25.0	
	(μg•h/ml)						
	AUC(0)	40.9±8.2	85.3±13.6	181±44.0	59.5±13.1	92.5±25.0	
	(µg•h/ml)						
	F _R (%)	-	92.3	_	64.4	-	

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10.2.3. BRIDGING PHARMACOKINETIC STUDY

Bridging pharmacokinetic studies were performed in order to compare the plasma pharmacokinetic profiles of the T1249 bulk drug substances used in the nonclinical trials described above to the formulated T1249 drug product which would be administered to an actual subject or patient, e.g., to treat HIV infection. The study was designed as a parallel group, one-way, cross-over comparison of three dose levels of T1249 bulk drug substance and three dose levels of formulated drug product. Plasma pharmacokinetics were assessed after single-25 dose administration and after steady state was achieved.

Administration of T1249 by subcutaneous injection resulted in measurable levels of peptide in all dose groups. The plasma concentration-time curves were roughly parallel within all dose groups following the initial dose (Days 1 and 15) and at steady state (Days 4 and 18) for both T1249 bulk.

30 drug substance and formulated T1249 drug product.

Furthermore $AUC_{(0-12hx)}$ values varied in direct proportion to

the dose level for both drug formulations. Calculated $AUC_{(0-12hr)}$ values for the drug product ranged from 43% to 80% of the $AUC_{(0-12hr)}$ values calculated for drug substance following single dose administration, and from 36% to 71% at steady state.

similar pharmacokinetic profiles in cynomolgus monkeys following bolus subcutaneous administration at the dose levels and dose volume tested. A direct comparison of the shapes of the plasma concentration-time curves in the present study and the shapes of curves from a previous study in cynomolgus monkeys suggests that there is a depot effect when T1249 is administered by subcutaneous injection. This is suggested by the increases in time at which maximal plasma concentration (tmax) is achieved and t1/2.

These results indicate that the formulation of bulk drug substance used in the pharmacology program yields comparable

15 AUC values and other kinetic parameters to those observed following the administration of the formulated drug product. These observations indicate that clinical administration of T1249 will result in total patient exposure to T1249.

The present invention is not to be limited in scope by
the specific embodiments described herein, which are intended
as single illustrations of individual aspects of the
invention, and functionally equivalent methods and components
are within the scope of the invention. Indeed, various
modifications of the invention, in addition to those shown
and described herein will become apparent to those skilled in
the art from the foregoing description and accompanying
drawings. Such modifications are intended to fall within the
scope of the appended claims.

WHAT IS CLAIMED IS:

1. A hybrid polypeptide comprising an enhancer peptide sequence linked to a core polypeptide.

- 2. The hybrid polypeptide of Claim 1, wherein the

 5 enhancer peptide sequence comprises: WXXWXXXI, WXXWXXXX,
 WXXWXX, WXXWX, WXXXW, WXXXWXWX, XXXWXWX, XXWXXWX, XWXXXX, WXXXXXW,
 WXXXXXWXW, WXXXXW, IXXXWXXW, XXXWXXW, XXXXXXW, XWXXXXW,
 XWXWXXXX, XWXWXX, XWXWX, XWXXXXW, WXWXXXXW or XWXXXXW.
- 3. The hybrid polypeptide of Claim 1 wherein the enhancer peptide sequence comprises WQEWEQKI or WASLWEWF.
 - 4. The hybrid polypeptide of Claim 1, wherein the enhancer peptide sequence is linked to the amino-terminal end of the core polypeptide.
- 5. The hybrid polypeptide of Claim 4, further comprising an enhancer peptide sequence linked to the carboxy-terminal end of the core polypeptide.
- 6. The hybrid polypeptide of Claim 1, wherein the enhancer peptide sequence is linked to the carboxy-terminal end of the core polypeptide.
 - 7. The hybrid polypeptide of Claim 1 wherein the core polypeptide is a therapeutic reagent.
- 8. The hybrid polypeptide of Claim 1 wherein the core polypeptide is a bioactive peptide, a growth factor, cytokine, differentiation factor, interleukin, interferon, colony stimulating factor, hormone or angiogenic factor amino acid sequence.
- 9. The hybrid polypeptide of Claim 1, wherein the core polypeptide comprises the following amino acid sequence: YTSLIHSLIEESQNQQEKNEQELLELDK; LEENITALLEEAQIQQEKNMYELQKLNS;

```
LEANISQSLEQAQIQQEKNMYELQKLNS; NNYTSLIHSLIEESQNQQEKNEQELLEL;
  DFLEENITALLEEAQIQQEKNMYELQKL; RYLEANISQSLEQAQIQQEKNMYELQKL;
  RYLEANITALLEQAQIQQEKNEYELQKL; NNYTSLIHSLIEESQNQQEKNEQELLELDK;
   TALLEQAQIQQEKNEYELQKLDK;
   TALLEQAQIQQEKNEYELQKLDE;
5 TALLEQAQIQQEKNEYELQKLIE;
   TALLEQAQIQQEKIEYELQKLDK;
   TALLEQAQIQQEKIEYELQKLDE;
   TALLEQAQIQQEKIEYELQKLIE;
   TALLEOAOIQOEKIEYELQKLE;
   TALLEOAQIQQEKIEYELQKLAK;
10 TALLEQAQIQQEKIEYELQKLAE;
   TALLEQAQIQQEKAEYELQKLE;
   TALLEQAQIQQEKNEYELQKLE;
   TALLEQAQIQQEKGEYELQKLE;
   TALLEOAOIQQEKAEYELQKLAK;
   TALLEQAQIQQEKNEYELQKLAK;
15 TALLEQAQIQQEKGEYELQKLAK;
   TALLEQAQIQQEKAEYELQKLAE;
   TALLEQAQIQQEKNEYELQKLAE;
   TALLEQAQIQQEKGEYELQKLAE;
   DEFDASISQVNEKINQSLAFIRKSDELL;
   DEYDASISQVNEKINQALAYIREADEL;
20 DEYDASISOVNEEINQALAYIRKADEL; DEFDESISOVNEKIEESLAFIRKSDELL;
   DEFDESISOVNEKIEESLAFIRKSDEL; or
   OHWSYGLRPG.
```

- 10. The hybrid polypeptide of Claim 9, wherein the enhancer peptide sequence is linked to the amino-terminal end of the core polypeptide.
 - 11. The hybrid polypeptide of Claim 10, further comprising an enhancer peptide sequence linked to the carboxy-terminal end of the core polypeptide.

12. The hybrid polypeptide of Claim 9, wherein the enhancer peptide sequence is linked to the carboxy-terminal end of the core polypeptide.

- 13. The hybrid polypeptide of Claim 9, wherein the enhancer peptide sequence comprises WQEWEQKI or WASLWEWF.
- 14. The hybrid polypeptide of Claim 9, wherein the hybrid polypeptide comprises the amino acid sequence: WQEWEQKITALLEQAQIQQEKNEYELQKLDKWASLWEWF, WQEWEQKITALLEQAQIQQEKIEYELQKLIEWEWF or VYPSDEYDASISQVNEEINQALAYIRKADELLENV.
 - 15. The hybrid polypeptide of Claim 14, further comprising an amino terminal acetyl group and a carboxy terminal amido group.
- 15 A core polypeptide comprising: YTSLIHSLIEESQNQQEKNEQELLELDK; LEENITALLEEAQIQQEKNMYELQKLNS; LEANISQSLEQAQIQQEKNMYELQKLNS; NNYTSLIHSLIEESQNQQEKNEQELLEL; DFLEENITALLEEAQIQQEKNMYELQKL; RYLEANISQSLEQAQIQQEKNMYELQKL; RYLEANITALLEQAQIQQEKNEYELQKL; NNYTSLIHSLIEESQNQQEKNEQELLELDK; TALLEQAQIQQEKNEYELQKLDK; 20 TALLEQAQIQQEKNEYELQKLDE; TALLEQAQIQQEKNEYELQKLIE; TALLEQAQIQQEKIEYELQKLDK; TALLEQAQIQQEKIEYELQKLDE; TALLEQAQIQQEKIEYELQKLIE; TALLEQAQIQQEKIEYELQKLE; 25 TALLEQAQIQQEKIEYELQKLAK; TALLEQAQIQQEKIEYELQKLAE; TALLEOAQIQQEKAEYELQKLE; TALLEQAQIQQEKNEYELQKLE; TALLEQAQIQQEKGEYELQKLE; TALLEQAQIQQEKAEYELQKLAK;

30 TALLEQAQIQQEKNEYELQKLAK;
TALLEQAQIQQEKGEYELQKLAK;

TALLEQAQIQQEKAEYELQKLAE;

TALLEQAQIQQEKGEYELQKLAE;

DEFDASISQVNEKINQSLAFIRKSDELL;

DEYDASISQVNEKINQALAYIREADEL;

DEYDASISQVNEEINQALAYIRKADEL;

DEFDESISQVNEKIEESLAFIRKSDEL;

OHWSYGLRPG.

- 17. The core polypeptide of Claim 16, further comprising an amino terminal acetyl group and a carboxy terminal amido group.
- 18. A method for enhancing the pharmacokinetic properties of a core polypeptide comprising linking a consensus enhancer peptide sequence to a core polypeptide to form a hybrid polypeptide, such that, when introduced into a living system, the hybrid polypeptide exhibits enhanced pharmacokinetic properties relative those exhibited by the core polypeptide.
 - 19. The method of Claim 18 wherein the core polypeptide is a therapeutic reagent.
 - 20. The method of Claim 18 wherein the core polypeptide is a bioactive peptide, growth factor, cytokine, differentiation factor, interleukin, interferon, colony stimulating factor, hormone or angiogenic factor.

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FIGURE 1

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FIGURE DA

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FIGURE 2B

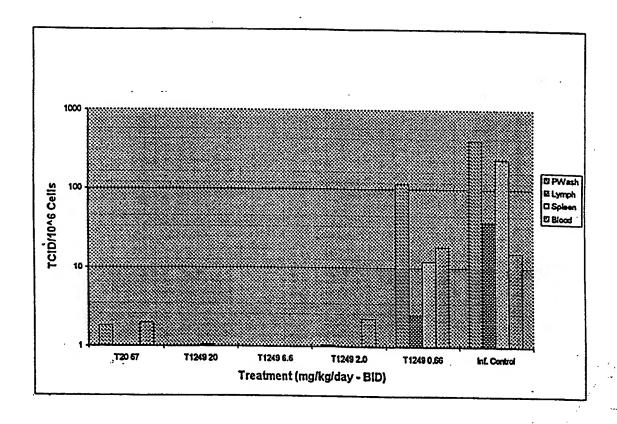


FIGURE 3

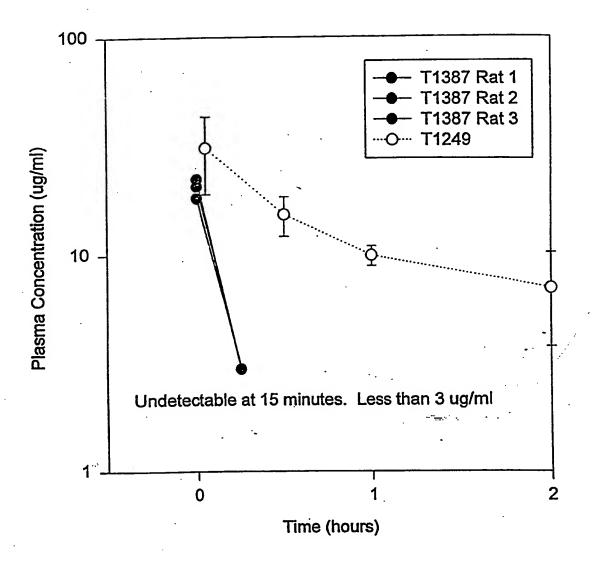


FIGURE 4A

5/23

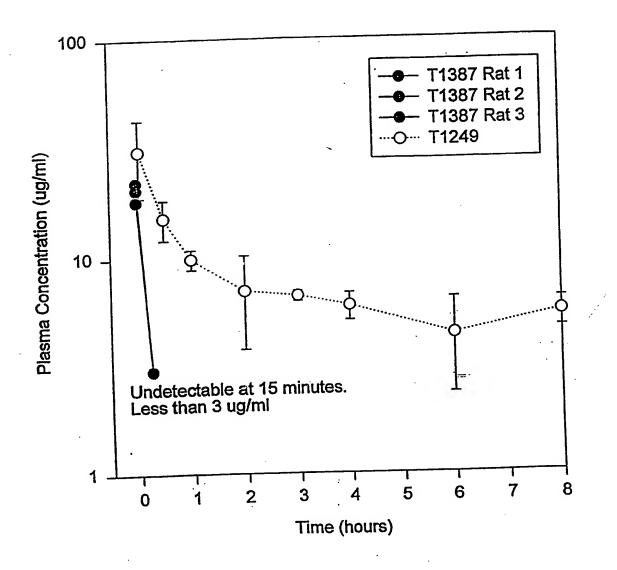
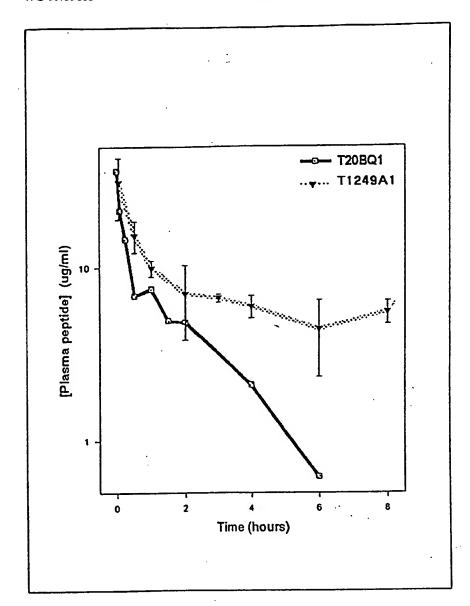


FIGURE 4B



Pharmacokinetic Parameters	T20BQ1	T1249A1
Dose (mg/kg·IV)	2.5	2.5
Detection method	Fluorescence	Fluorescence
	HPLC	HPLC
Tarra (11)	1.6	4.71
Cl. (ml/h)	27.94	9.62
AÚĠ ₍₀₋₈₎ (ug:h/ml)	26.12	71.43

FIGURE 5

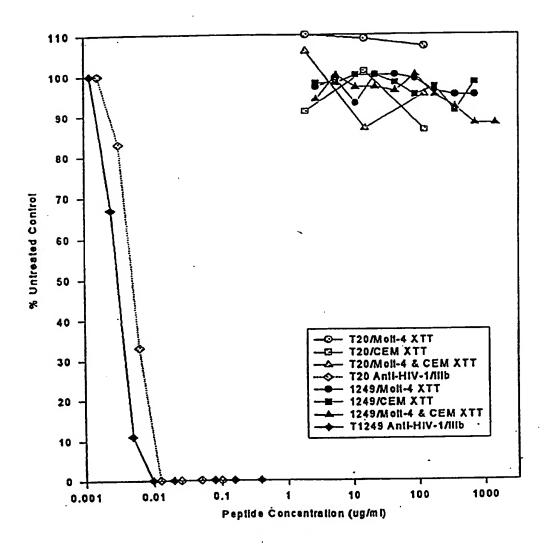


FIGURE 6

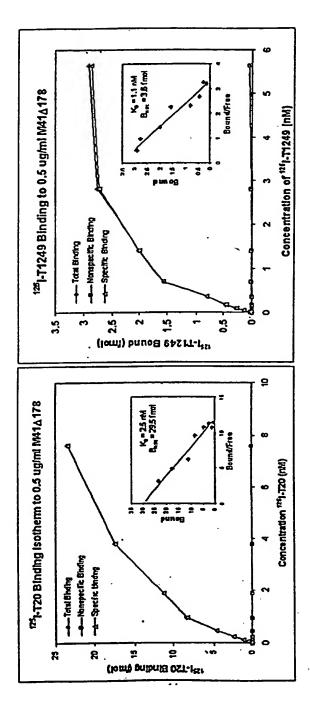


FIGURE 7

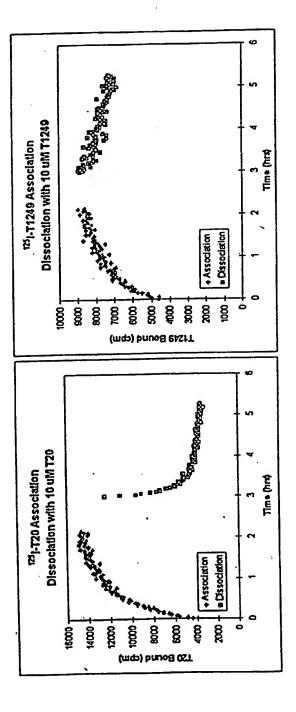
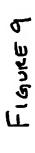
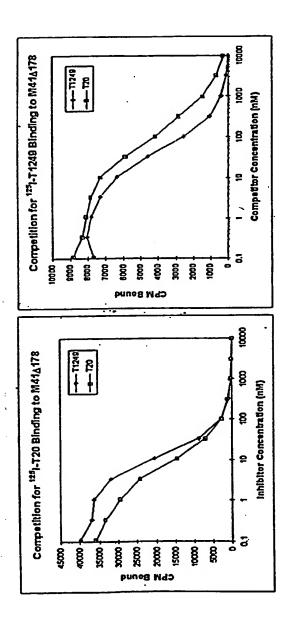


FIGURE B





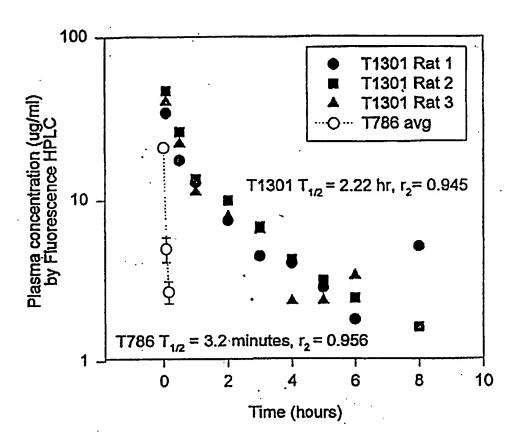


FIGURE IDA

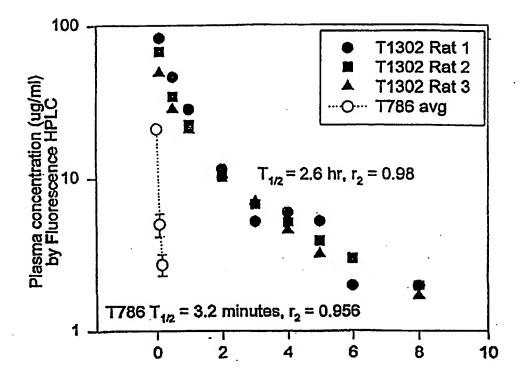


FIGURE LOB

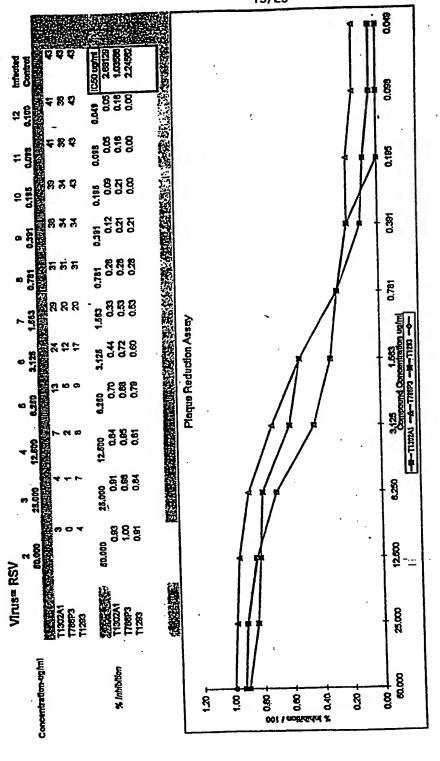


FIGURE 11A

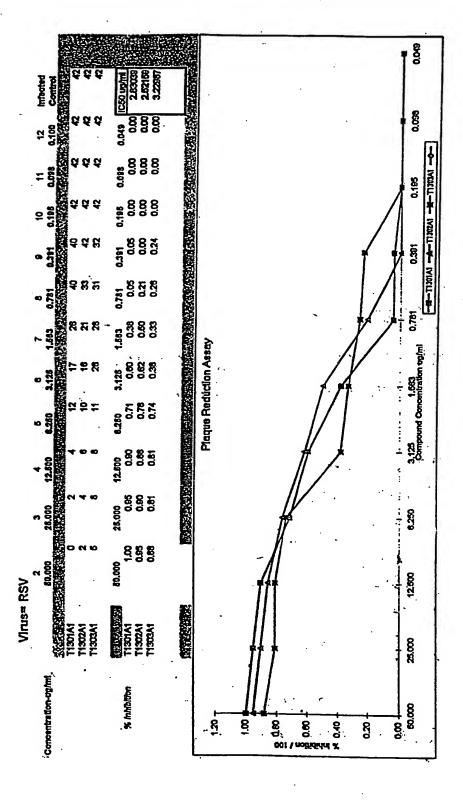


FIGURE 11 B

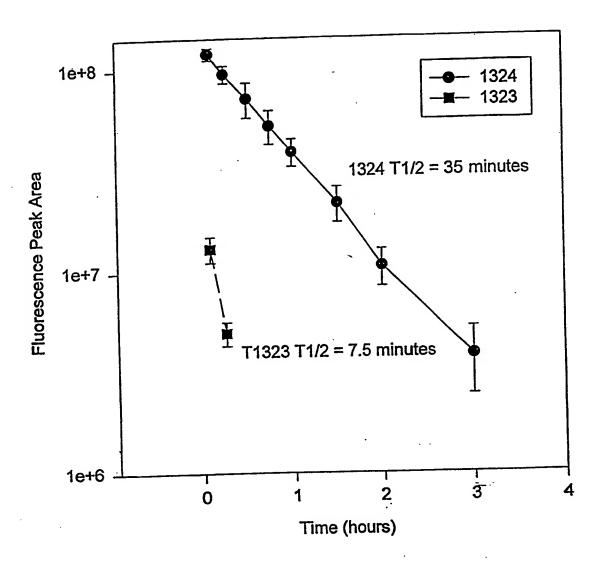


FIGURE 12A

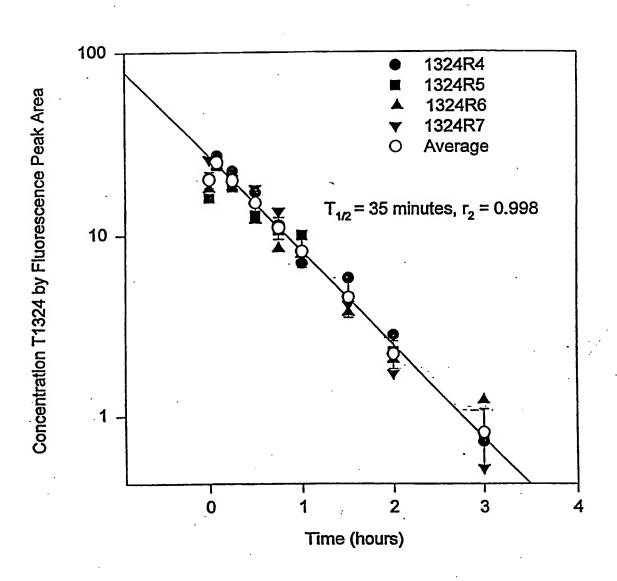


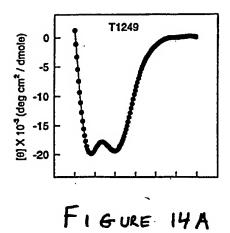
FIGURE 12B

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FIGURE 13 contid,



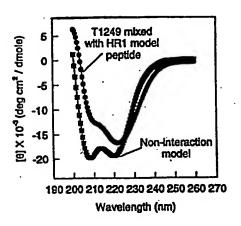


FIGURE 14B

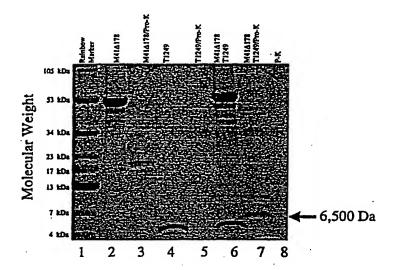


FIGURE 15

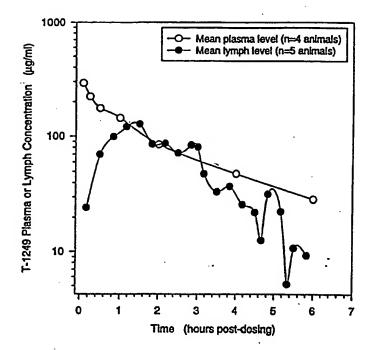


FIGURE 16C

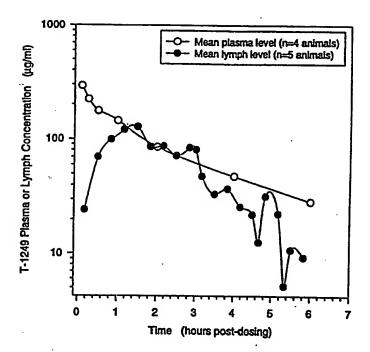


FIGURE 16C

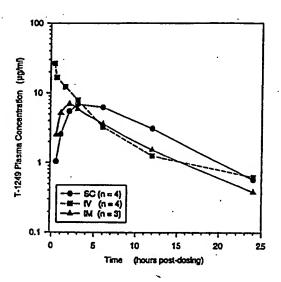


FIGURE 17A

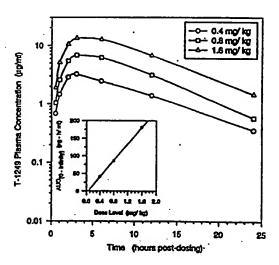


FIGURE 17B

INTERNATIONAL SEARCH REPORT

International application No. PCT/US99/11219

	SSIFICATION OF SUBJECT MATTER		٠-
	Please See Extra Sheet.		
US CL :	Please See Extra Sheet. International Patent Classification (IPC) or to both r	national classification and IPC	
	DS SEARCHED		
Minimum do	ocumentation searched (classification system followed	by classification symbols)	
U.S. :	530/300, 313, 324, 326, 328, 350, 397, 398, 399; 514	4/2, 12, 13, 15	
Documentati	ion searched other than minimum documentation to the	extent that such documents are included	in the fields searched
Electronic d	ata base consulted during the international search (na	me of data base and, where practicable	, search terms used)
APS, GE	NESEQ, SWISSPROT, PIR, STN ms: hybrid, chimeric, sequences of claims 9 and 16		
C. DOC	UMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where app	propriate, of the relevant passages	Relevant to claim No.
х	US 5,723,129 A (POTTER ET AL) abstract, column 4, lines 36-43, SEQ 3953-962.		1, 4, 7-10, 16, 18-20
X,P	US 5,763,160 A (C. WANG) 09 June line 60 - column 10, line 39, column 41, column 18, line 65 - column 19, l 64.	15, line 25 - column 16, line	1, 6-8, 18-20
X,P	US 5,843,913 A (LI ET AL) 01 Decem 2, SEQ ID NO:2. especially residues 3		16
х	EP 0 272 858 A2 (REPLIGEN COR (29/06/88), page 9, line 54 - page 10, 18, lines 11-15, Table 3.		1, 2, 4-12, 16, 18-20
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<u> </u>	ner documents are listed in the continuation of Box C		and the data and sinks
'	ecial categories of cited documents: cument defining the general state of the art which is not considered	"T" later document published after the int date and not in conflict with the app the principle or theory underlying th	lication but cited to understand
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•P• do	cument published prior to the international filing date but later than a priority date claimed	'&' document member of the same pater	nt family
Date of the	actual completion of the international search	Date of mailing of the international se 21 OCT 19	
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INTERNATIONAL SEARCH REPORT

International application No. PCT/US99/11219

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 306 912 A2 (ALBANY MEDICAL COLLEGE) 15 March 1989 (15/03/89).	1-20
X	EP 0 578 293 A1 (AKZO N.V.) 12 January 1994 (12/01/94), page 3, lines 35-58, page 4, lines 45-49.	1, 2, 4-12, 16, 18- 20
x	WO 91/07664 A1 (CAMBRIDGE BIOSCIENCE CORPORATION) 30 May 1991 (30/05/91), page 4, lines 17-26, page 10, lines 9-17, Examples 3 and 4, Figures 4, 8, 12, 15, and 21.	1, 2, 4, 6-8, 18-20
A	WO 91/09872 A3 (UNIVAX BIOLOGICS, INC.) 11 July 1991 (11/07/91).	1-20
X	WO 93/14207 A1 (CONNAUGHT LABORATORIES LIMITED) 22 July 1993 (22/07/93), abstract, Figures 1 and 5.	1, 4, 7-10, 16, 18 20
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INTERNATIONAL SEARCH REPORT

International application No. PCT/US99/11219

A. CLASSIFICATION OF SUBJECT MATTER: IPC (6):	
A61K 38/02, 38/08, 38/10, 38/16, 38/18, 38/19, 38/22; C07K 7/06, 7/08, 14/00	
A. CLASSIFICATION OF SUBJECT MATTER: US CL :	
530/300, 313, 324, 326, 328, 350, 397, 398, 399; 514/2, 12, 13, 15	
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